

American Journal
of
Digestive Diseases
Volume 12

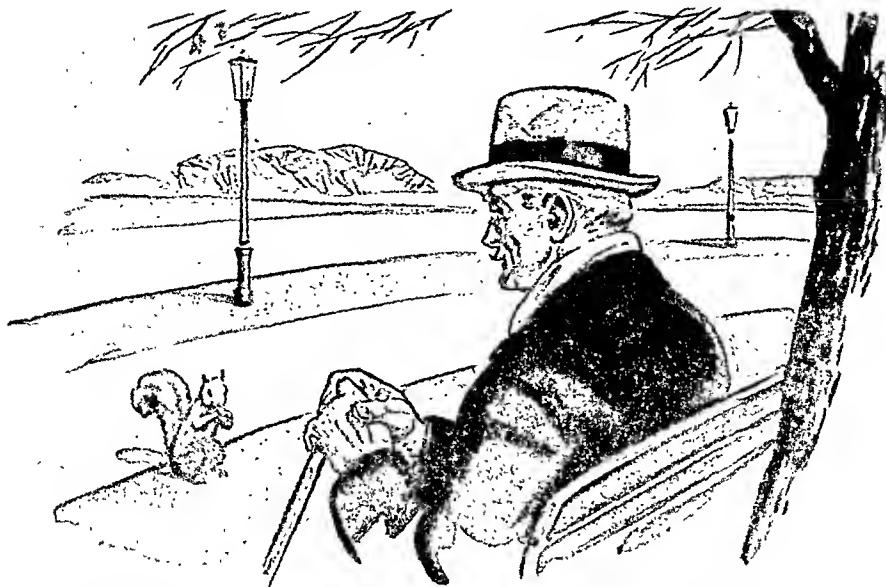
The American Journal of DIGESTIVE DISEASES

An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

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ESPECIALLY ADVANTAGEOUS *for the Aged*

Adequate strength can be maintained, and the manifestations of senescence can be postponed until ripe old age, if nutritional requirements are properly met. But to accomplish this aim with ordinarily eaten foods alone, frequently proves difficult.

As the years advance, certain foods are less easily digested. In many instances, organic and functional affections not only lessen the appetite, but also impair the powers of digestion and absorption. In consequence the aged usually impose diets upon themselves which perforce cannot meet the nutritional requirements.

Ovaltine, a delicious food drink, made with milk

as directed, proves especially advantageous for the aged. It supplies virtually every essential nutrient in readily metabolized form: biologically adequate protein, readily utilized carbohydrate, well-emulsified fat, all the essential vitamins except vitamin C, and the important minerals. How readily three glassfuls of Ovaltine daily can bring the intake of essential food factors to optimal levels, is indicated by the analysis here shown.

Ovaltine is digested with remarkable ease. Its low curd tension makes for rapid gastric emptying. Its appealing taste is relished by the aged as well as by younger persons.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.



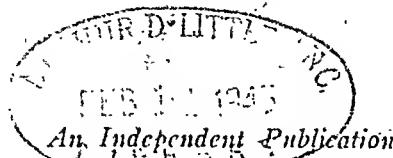
Ovaltine

Three daily servings of Ovaltine, each made of
½ oz. Ovaltine and 8 oz. of whole milk,* provide:

PROTEIN	31.2 Gm.	VITAMIN A	2953 I.U.
CARBOHYDRATE	62.43 Gm.	VITAMIN D	480 I.U.
FAT	29.34 Gm.	THIAMINE	1.296 mg.
CALCIUM	1.104 Gm.	RIBOFLAVIN	1.278 mg.
PHOSPHORUS903 Gm.	NIACIN	7.0 mg.
IRON	11.94 mg.	COPPER5 mg.

*Based on average reported values for milk.

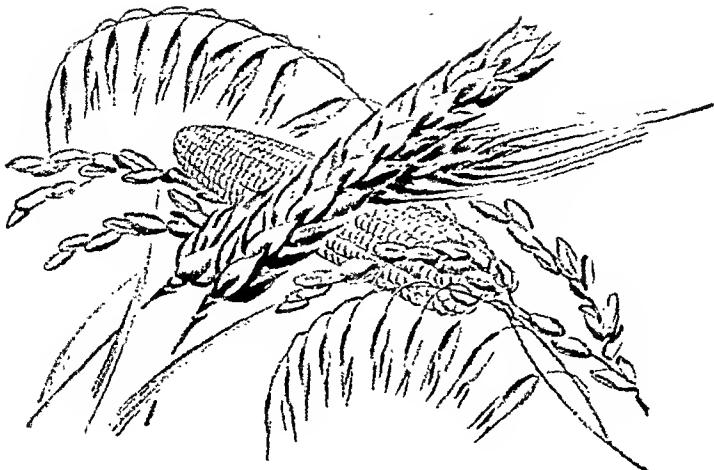
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In the Dietary Adjustments Demanded by Gastrointestinal Disease

The four characteristics of the dietary called for in gastrointestinal disease—blandness, low in inert residue, nutritional balance, and acceptability—are also the characteristics of a wide variety of cereals when eaten with whole milk and sugar. Hence cereals may well form an integral and important part of the G.I. patient's food.

The dish so composed is thoroughly bland; it does not lead to an undue outpouring of acid gastric juice; it is digested with ease and its stay in the stomach is comparatively short.

Cereals (except those purposely made different through bran content) are digested almost quantitatively. There is little residue to prove a burden in the intestinal tract.

Nutritionally, the dish of cereal (whole-grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), milk, and sugar shows a composition of basic and auxiliary nutrients

bettered by few other foods. It contributes biologically adequate protein, carbohydrate, and easily emulsified fat, important vitamins, and essential minerals. The quantitative contribution of this dish—1 oz. of cereal, 4 oz. of whole milk, and 1 teaspoonful of sugar—is shown in the appended table.

Cereals are acceptable to virtually all patients. Their variety of taste and form is so great that the patient need never tire of them, though they may be served several times daily.

Calories.....	201
Protein.....	7 Gm.
Carbohydrate.....	32 Gm.
Fat.....	5 Gm.
Thiamine.....	0.19 mg.
Riboflavin.....	0.27 mg.
Niacin.....	1.82 mg.
Calcium.....	158 mg.
Iron.....	1.73 mg.



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WHEN NUTRITION MUST BE MAINTAINED

Few are the diseases in which maintenance of the nutritional state is less important than specific therapy. For unless the metabolic demands are adequately satisfied, maximal response to drug administration hardly can be expected.

In a host of febrile, infectious, and neoplastic diseases Ovaltine can be of considerable benefit in supplying the extra nutrients required during periods of greater need. This nutritious food

drink, made with milk, supplies the dietary elements required: adequate protein, readily assimilated carbohydrate, B complex and other vitamins, as well as important minerals. Ovaltine leaves the stomach rapidly because of its low curd tension, hence may be taken as frequently as deemed necessary. And its delicious taste encourages adequate consumption, an important factor in combating the anorexia of many diseases.

THE WANDER COMPANY, 360 NORTH MICHIGAN AVENUE, CHICAGO 1, ILLINOIS



Ovaltine

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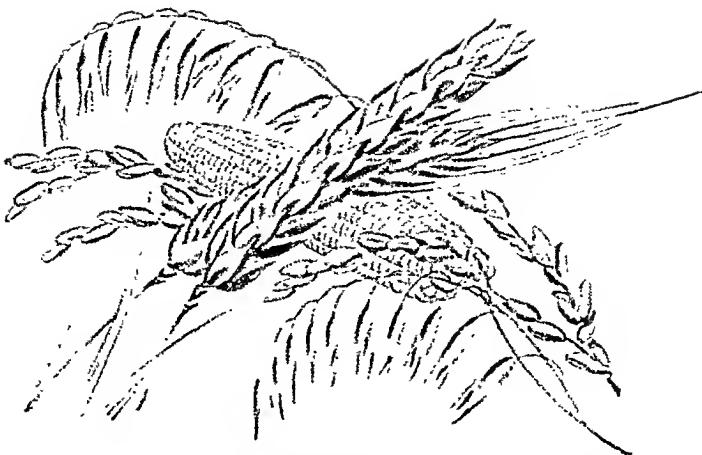
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In the So-Called Syndrome of "Spastic Colitis"

In the dietary called for by spastic colitis—so frequently accompanied by reflex gastric involvement and dyspepsia—cereals have a well-merited place, whether of the ready-to-eat or to-be-cooked variety.

Nutritionally, the dish composed of 1 oz. of cereal (whole-grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), 4 oz. of milk, and 1 teaspoonful of sugar presents a composition of basic and auxiliary nutrients bettered by few other foods. The appended table of composite averages shows the quantities of each of the essential nutrients contained.

Except for those made purposely different through bran content, cereals are digested almost quantitatively. There is little inert residue

which might prove offensive to the spastic colon. The combination of cereal, milk and sugar is dependably bland. It does not lead to an undue outpouring of acid gastric juice. Its stay in the stomach is comparatively short, and it is digested with ease.

The wide variety of cereals available assures that this one component of the spastic colitis diet need never become tiresome for the patient.

Calories	201
Protein.....	7 Gm.
Carbohydrate.....	32 Gm.
Fat.....	5 Gm.
Thiamine.....	0.19 mg.
Riboflavin.....	0.27 mg.
Niacin.....	1.82 mg.
Calcium.....	158 mg.
Iron.....	1.73 mg.



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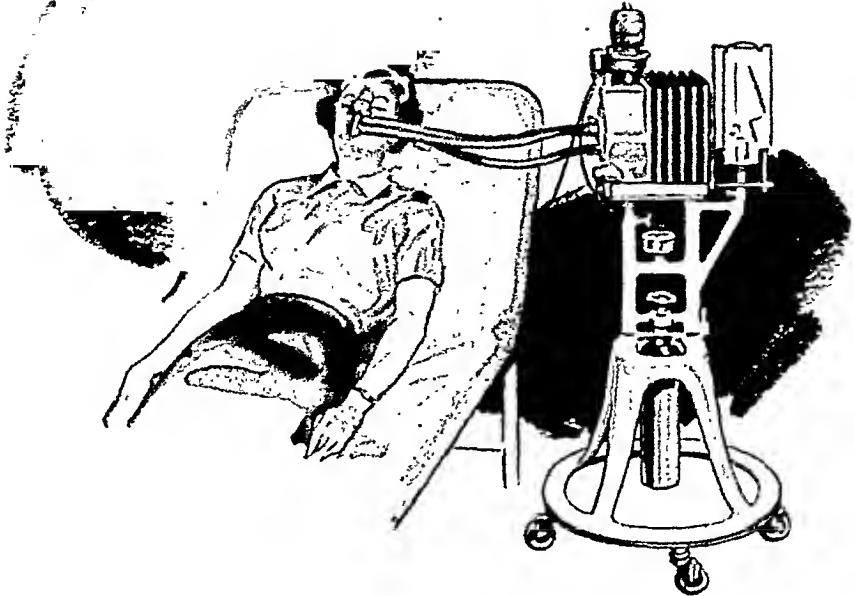
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In Hyperthyreosis, too

The symptom complex of increased appetite, exaggerated psychomotor tension, hyperhidrosis, and loss of weight, in addition to spelling thyrotoxicosis, also reflects the intense metabolic activity characteristic of this condition. Utilization of nutrients may be 50 per cent above normal.

Whether therapy be conservative or surgical, metabolic deficits must be eradicated and some of the consumed body tissue restated. To this end the intake of virtually all essential nutrients must

be doubled. If surgery is contemplated, nutritional preparation ranks in importance with iodine preparation for a successful outcome.

Ovaltine can be a valuable component of the high-caloric, high-vitamin diet required in hyperthyreosis. This delicious food drink, made with milk, not only increases the caloric intake appreciably, but also significantly augments the intake of complete proteins and of vitamins and minerals, all of which are required in added amounts.

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CALCIUM	1.104 Gm.	RIBOFLAVIN	1.278 mg.
PHOSPHORUS903 Gm.	NIACIN	7.0 mg.
IRON	11.94 mg.	COPPER5 mg.

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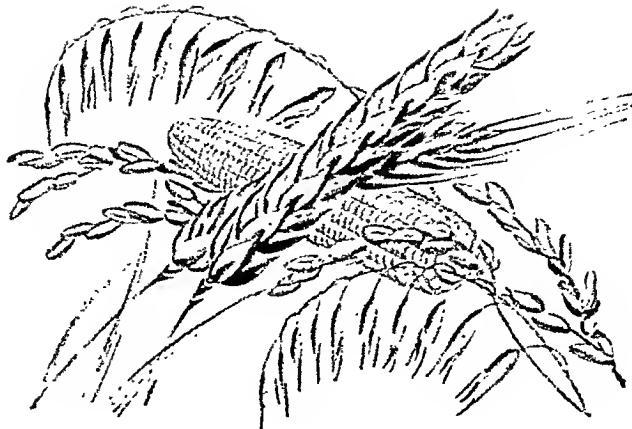
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In the Specific and Non-Specific Intestinal Affections

The common denominator of therapy in many specific and non-specific intestinal affections is the dietary which is called for as soon as solid foods can be permitted. The diet must be bland—it must not evoke an undue amount of acid gastric secretion—it must be low in residue—must be of good nutritional "balance"—must be acceptable to the patient to combat the usually severe anorexia. Cereals, ready-to-eat or to-be-cooked, eaten with milk and sugar, fit well into such a dietary.

Except those made purposely different through bran content, cereals are dependably bland. They leave little inert residue. Nutritionally, the dish composed of 1 oz. of cereal (whole-grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), 4 oz. of milk, and 1

teaspoonful of sugar presents a combination of basic and auxiliary nutrients bettered by few other foods. The appended table of composite averages shows the quantities of each of the essential nutrients contained.

Their pleasingly neutral taste makes cereals readily acceptable to virtually all patients. Their wide variety is assurance that they can be given several times daily if need be, without jading the appetite for one particular kind.

Calories.....	201
Protein.....	7 Gm.
Carbohydrate.....	32 Gm.
Fat.....	5 Gm.
Thiamine.....	0.19 mg.
Riboflavin.....	0.27 mg.
Niacin.....	1.82 mg.
Calcium.....	158 mg.
Iron.....	1.73 mg.



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When Weight Gains ARE NEEDED

To the underweight patient just recovered from severe acute or chronic illness, increase in weight may be difficult to achieve. Yet restoration of normal fat deposits and correction of nutritional deficiencies are essential for rapid return of strength and resistance to infection.

The intake of essential nutrients high in calorific value is expeditiously accomplished by including Ovaltine in the diet. This tasty food drink, made with milk as directed, is

enjoyed by all patients both as a mealtime beverage and between meals. Not only rich in calories, it also provides generously other nutrients urgently required: biologically adequate proteins, highly emulsified fats, B complex and other viramins, as well as the essential minerals iron, copper, calcium and phosphorus. The low curd tension of Ovaltine favors quicker gastric emptying, hence appetite is actually enhanced through this desirable behavior.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.



Ovaltine

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CARBOHYDRATE	62.43 Gm.	VITAMIN D	480 I.U.
FAT	29.34 Gm.	THIAMINE	1.296 mg.
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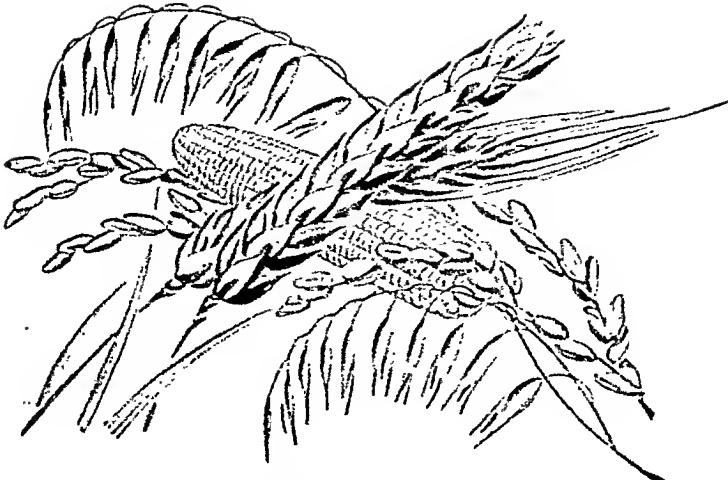
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In the Dietary of the Hepatobiliary Patient

Advancing knowledge of nutritional requirements during disease has considerably changed the concept of the dietary adjustment called for in hepatobiliary disease. The need for protein heretofore has been greatly underestimated. Today it is recognized that an adequate supply of protein, together with an ample amount of carbohydrate, affords maximal protection for the liver. Fat, it is stated, need not be omitted; it should be given in small amounts, and in the most digestible form.

Since the auxiliary nutrients required during health must also be supplied during biliary tract disturbances, cereals—ready-to-eat or to-be-cooked—fit well into the diet called for by the hepatobiliary syndrome.

The dish of cereal, composed of 1 oz. of cereal (whole-grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), 4 oz. of whole milk, and 1 teaspoonful of sugar, presents a

nutritional composition bettered by few foods. It is high in desirable carbohydrate. Its proteins, derived from cereal and milk, contain no hepatotoxic extractives, and are of excellent biological value. Its fat is readily emulsified. In addition it provides important minerals and B vitamins. Blandness and easy digestibility, together with a wide variety of taste and form, make cereals acceptable to the patient, even when served several times daily.

The appended table of composite averages shows the quantities of the essential nutrients contained.

Calories.....	201
Protein.....	7 Gm.
Carbohydrate.....	32 Gm.
Fat.....	5 Gm.
Thiamine.....	0.19 mg.
Riboflavin.....	0.27 mg.
Niacin.....	1.82 mg.
Calcium.....	158 mg.
Iron.....	1.73 mg.



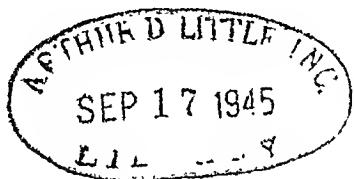
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The American Journal of **DIGESTIVE DISEASES**

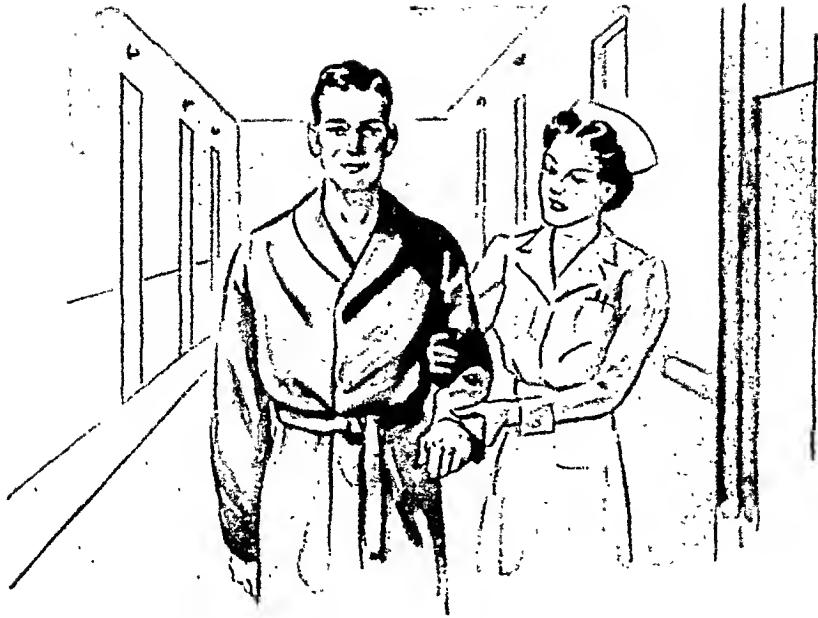
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DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION



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NUTRITION AND THE TIME FACTOR *in Convalescence*

Febrile and certain metabolic diseases impose a serious drain on the nutritional reserves of the organism. The need for virtually all nutrients is increased considerably, far beyond the point where dietary adjustment can be expected to compensate. Hence, as convalescence begins, the incurred nutritional deficit must be made good before complete recovery can ensue. The more quickly nutritional deficiencies are corrected, the more quickly will convalescence progress to complete return of normal strength and vigor.

The use of Ovaltine, made with milk as di-

rected, helps to raise the convalescent's intake of essential nutrients to desired levels. This delicious food drink provides biologically adequate protein, readily assimilated carbohydrate, highly emulsified fat, B complex and other vitamins, and essential minerals. Its low curd tension makes for quicker gastric emptying, hence it does not cloy the appetite. Ovaltine breaks the monotony of many diets and its attractive, appealing taste assures its acceptance by the patient. Hence Ovaltine may be given in the recommended three glassfuls daily for maximum benefit.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.



Ovaltine

Three daily servings of Ovaltine, each made of
½ oz. Ovaltine and 8 oz. of whole milk,* provide:

PROTEIN	31.2 Gm.	VITAMIN A	2953 I.U.
CARBOHYDRATE	52.43 Gm.	VITAMIN D	480 I.U.
FAT	29.34 Gm.	THIAMINE	1.296 mg.
CALCIUM	1.101 Gm.	RIBOFLAVIN	1.275 mg.
PHOSPHORUS903 Gm.	NIACIN	7.0 mg.
IRON	11.94 mg.	COPPER5 mg.

*Based on average reported values for milk.

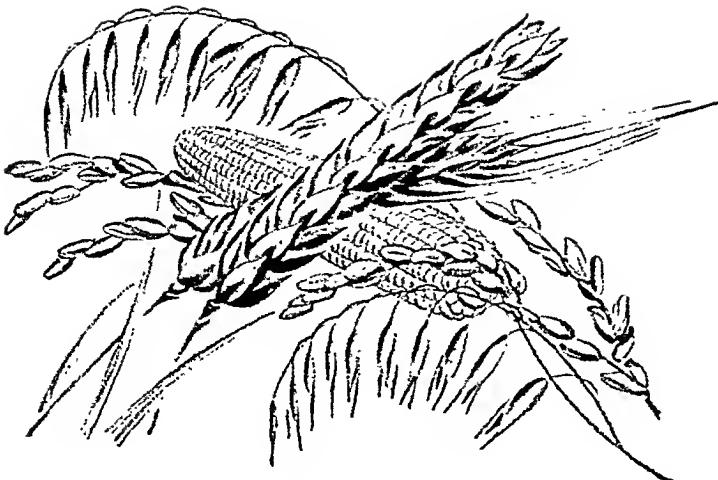
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A Wealth of Essential Nutrients in a Thoroughly Bland Form

In the dietary adjustment called for by gastro-intestinal disease, cereal—whether of the ready-to-eat or to-be-cooked variety—presents four distinct advantages:

(1) The dish composed of cereal (whole-grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), milk, and sugar, presents a nutritional composition bettered by few foods. It provides biologically adequate protein, carbohydrate, easily emulsified fat, B vitamins, and minerals, the nutrients especially important after surgery.

(2) It is dependably bland, does not evoke an undesirable amount of acid gastric juice, and is digested with ease.

(3) Except in the case of cereals purposely made different through bran content, it is digested almost

quantitatively. There is little inert residue which might prove burdensome to the patient's intestinal tract.

(4) Cereals are available in such a wide variety of taste and form that one or the other—if not all of them—is readily accepted by the patient, even if given several times daily.

The nutritional contribution made by 1 oz. of cereal, 4 oz. of milk, and 1 teaspoon of sugar is shown by the appended table of composite averages:

Calories.....	202
Protein.....	7.1 Gm.
Fat.....	5.0 Gm.
Carbohydrate.....	33 Gm.
Calcium.....	156 mg.
Phosphorus.....	206 mg.
Iron.....	1.6 mg.
Thiamine.....	0.17 mg.
Riboflavin.....	0.24 mg.
Niacin.....	1.4 mg.



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Not Merely ISOLATED NUTRIENTS

Essential though they are, vitamins are nevertheless not the only nutrients which may be lacking in the diet of persons physically below par. Nutritional imbalance, not infrequently the cause of poor physical stamina, excessive irritability, and poor appetite, may be attributable to other dietary-induced deficiencies. In consequence, adjustment of the entire nutritional intake is indicated.

Virtually any diet can be enhanced to a point of adequacy through the addition of three glassfuls of Ovaltine daily. Made with milk as

directed, this delicious food drink supplies liberal quantities of most essential nutrients, as indicated by the table below. Qualitatively Ovaltine is equally valuable; it provides biologically adequate protein, readily assimilated and utilized carbohydrate, well emulsified fat, B complex and other vitamins, as well as essential minerals. Ovaltine proves advantageous both as a mealtime beverage and a between-meal snack. Its low curd tension insures rapid gastric emptying, hence it does not interfere with the appetite for the next meal.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.



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Three daily servings of Ovaltine, each made of
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*Based on average reported values for milk.

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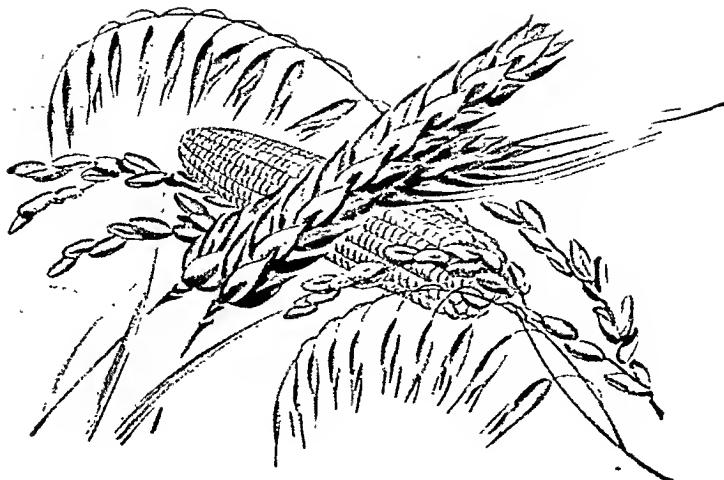
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Few Other Foods Can Better This Nutritional Composition

Much has been learned during the recent past about the nutritional needs of the aged. The importance of an adequate morning meal has gained wide recognition. That breakfast should be adequate not only calorically, but also in its content of essential nutrients, has been advocated by medical as well as nutritional authorities.

In the breakfasts recommended for those of advancing age, cereals, ready to eat or to be cooked, occupy an important place. For there are few foods that can better the nutritional composition of the dish composed of cereal, milk, and sugar.

Besides quickly available food energy, this dish provides notable amounts of biologically adequate

protein, the essential B vitamins thiamine, riboflavin, and niacin, and important minerals.

The nutritional contribution made by 1 oz. of cereal (whole-grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), 4 oz. of milk, and 1 teaspoonful of sugar, is shown in this table of composite averages:

Calories.....	202
Protein.....	7.1 Gm.
Fat.....	5.0 Gm.
Carbohydrate.....	33 Gm.
Calcium.....	156 mg.
Phosphorus.....	206 mg.
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A Fasting-Blood-Sample Procedure in the Differential Diagnosis and Management of Hepatic Disease

By

DAVID SCHWIMMER, M.D.**

S. D. KLOTZ, M.D.***

I. J. DREKTER, B.S.

THOMAS H. McGAVACK, M.D.

NEW YORK, N. Y.

THE manifold functions of the liver have resulted in the development of a wide variety of tests designed to appraise one or more of its activities. Some are intended for differential diagnosis, others for estimation of hepatic reserve, and still others for study of liver physiology. So great is the number of these tests and so complicated are some that their employment in everyday practice is decidedly limited. Therefore, it has seemed worthwhile to present, in some detail, data obtained by us over a period of four years in the use of informative tests which can be performed on a single fasting specimen of blood. This is an amplification of a preliminary report already made by one of us (S.D.K.) (1).

The single-specimen group of tests, to which we shall for brevity refer as the "composite-test", adapts itself readily to any hospital routine, as well as to the needs of the private practitioner, and through several years has afforded a number of very definite practical advantages over any other approach we have been able to make on this subject: (1) a minimum of discomfort to the patient, (2) a distinct economy of both patient's and physician's time, (3) the elimination of personal factors of error—only two people at most need be involved in the collection of the sample and in the performance of the tests, (4) the relative simplicity of the laboratory procedures, (5) the ease with which the entire group of tests may be repeated, and (6) the readiness with which serial, and often single, determinations afford a "cross-section" of the hepato-biliary status in any given individual.

A number of currently popular tests, such as the hippuric-acid excretion, involve determinations of urinary concentrations: obviously these will be modified by the patient's renal status and therefore frequently will be difficult to interpret, especially since renal dysfunction is so often concomitant with hepatic disease. Others, such as the bromsulphalein, have limited value in the presence of jaundice or lipemia. Many of these tests, too, demand multiple venipuncture and the withholding of oftentimes important therapy for a matter of several hours; our method calls for a single venipuncture,

which does not in any way interfere with the regimen of the day. For the performance of tests in which preparatory drugs—such as rose bengal, bromsulphalein, galactose, and benzoic acid—are used, urine specimens must be saved and/or blood specimens must be taken on a carefully planned time-schedule. Where whole blood is employed, care must be taken that the blood and anti-coagulant are well-mixed; our tests, done on serum, avoid the need for such precaution.

It can be seen, then, that there are many opportunities for error, if only because many hands are involved, both on the ward and in the laboratory. The single-specimen method removes most of these, and moreover enables a single laboratory technician to supervise directly each of the individual tests. Thus "personal factors of error" are minimized or totally avoided. The actual performance of the tests in the laboratory is relatively simple, and, in an emergency, all save the cephalin-cholesterol flocculation can be completed within a three-hour period. For the above reasons multiple observations can be made without serious discomfort to the patient and with a minimum of work on the part of clinician and laboratory technician.

TESTS USED

In selecting tests for "liver function", one must perforce bear in mind the complex physiology of the liver, its enormous reserve power and regenerative capacity, the selectively damaging action of certain diseases and toxic agents, and, finally, the purpose and sensitivity of the tests themselves.

As in the case of cardiac disease, the tremendous reserve power or "safety factor"—so important for the welfare of the patient—has been the stumbling block in the way of devising a test which adequately pictures the overall hepatic status. Structurally or functionally, a destruction or inhibition of a large part of the hepatic parenchyma may occur before some of the tests currently used will uncover an insufficiency.

The liver is not a static, but a dynamic organ, and its physiology is as complex as the number of bodily processes in which it plays a part. The suppression of one function does not necessarily cause an interference with any or all other activities. For example, in lipoic acid deficiency, fatty infiltration occurs; in this situation there is interference with the removal of the dye bromsulphalein, but no detectable disturbance of bile excretion or vitamin K synthesis. This "dissociation of the functions of the organ" (2) necessitates the use of multiple tests for any adequate appraisal of its status.

* From the Department of Medicine, Lynn J. Boyd, M. D., Director; and the Department of Pathology, A. Saccone, M. D., Director; Metropolitan Hospital; and the New York Medical College.

** Fellow in Internal Medicine, New York Medical College; Assistant Clinical Visiting Physician (Research Unit), Metropolitan Hospital. Participation in this study is in partial fulfillment of requirements for the degree of Master of Medical Science in Medicine.

*** Now serving with the United States Army, Medical Corps. Presented in part before the Clinical Session of the New York Academy of Medicine Graduate Fortnight, October, 1943. Submitted June 23, 1944.

4 Group I, those conditions which are primarily intrahepatic, such as hepatitis, cirrhosis, fatty degeneration, and neoplasms; comprised 47.3% (355 cases). Group II, the extra-hepatic obstructions, including neoplasms, lithiasis, and stricture of the common duct, represented 12.7% (95 cases). Group III, the hemolytic processes, consisting of anemias and infarctions, totaled 6.1% (46 cases). Group IV, the remaining 33.9% (254 cases), included a heterogeneous assortment of diseases primary elsewhere in the body, but capable of secondarily affecting the liver.

Of particular interest among our cases have been such rarities as hepatitis caused by stilbestrol (9), brucellosis (10), trichinosis, infectious mononucleosis, typhoid vaccine, and sickle-cell anemia.

Care was taken to substantiate the diagnosis in each case reported. More than 100 cases were discarded because it was believed the available data was insufficient for satisfactory classification. Of those reported, in 35% the diagnoses were verified by autopsy, operation, biopsy, peritoneoscopy, or some combination of these; in 65%, by history, clinical findings and course, and roentgenologic studies. Furthermore, in over 50% of the cases, there were performed one or more concomitant tests, such as the prothrombin estimation, galactose tolerance, modified glucose tolerance, bromsulphalein retention, hippuric acid excretion, Weltmann and Takata-Ara reactions, amylase and lipase levels, duodenal drainage, and urinary and fecal bile and urobilinogen determinations—all with a view to determining the relative accuracy and delicacy of these tests and of our own procedure.

Methods.

The routine tests performed on each patient have already been mentioned. A normal range of values for each test as performed in our laboratory was obtained by trials of the series in 100 patients known not to have any hepatic or other disease which would be expected to exert an abnormal influence upon the result. These values are listed in Table II.

That all these tests can be performed on the serum obtained from only 12 cc. of clotted blood is due to the use of modified technics, to be described below. The choice of methods was frequently directed, as will be indicated, by the easy availability of reagents commonly used in other tests routine in our laboratory, and by the opportunity to incorporate other tests routinely done. Wherever colorimetric methods were adaptable, the Klett-Summerson photoelectric colorimeter was employed. It is of interest to note, when evaluating the uniformity and accuracy of these procedures, that they were all done either by, or under the direction of, a single chemist.

Preparation of Blood Specimen—Twelve cc. of blood were withdrawn from one of the arm veins of the fasting patient. To avoid any hemolysis, a dry syringe and needle were used, and the blood was not allowed to foam either in the syringe or on delivery into a dry test tube. The blood was then centrifuged, the supernatant serum was removed by pipette and all the tests were performed on the serum.

Icteric Index—Meulengracht's original method (11) was modified by diluting 0.5 cc. of serum (instead of 1.0 cc.) to 10 cc. with physiologic saline. Direct reading was then made in the photoelectric colorimeter.

Vit. den Bergh—*Direct*—This test was performed in the usual manner (12), save that 0.5 cc. of serum instead of 1.0 cc. was used. The readings with this are of three kinds: 1) Direct Immediate—color changes immediately, 2) Direct Delayed—no immediate result; color changes after standing, 3) Direct Biphasic—color changes immediately, but deepens on standing.

Cephalin-Cholesterol Flocculation—The procedure originally described by Hanger (13) was used. As no commercial cephalin was available when we first employed this test, we made our own from sheep's brains and have continued to do so. Especial care was taken in the preparation of the cephalin, the procedure being similar to that described by Thudichum (14). New reagent was prepared at least once weekly, as has been suggested by others (15). It was preserved at ordinary refrigerator temperature. Aging of the cephalin was not found important in the avoidance of false positive reactions. Of more importance was the method of reading the tests: only those reactions were considered positive wherein the flocculum was sufficiently marked to cause settling to the bottom of the tube.

Phosphatase (Alkaline)—The method of Bodansky (16) was employed, with the exception that 0.2 cc. of serum was substituted for the originally recommended 1.0 cc. It was realized that the King-Armstrong method might be more suitable, as no determination of phosphorus need then be done, but since the estimation of phosphorus is one of our laboratory routines, it was decided to employ the same reagents for the Bodansky procedure. The incidentally obtained value for phosphorus may afford a sidelight on the patient's renal status and on occasion reveals unexpected pathology. Furthermore, a simple modification of the Bodansky method (adjusting the buffer) permits determination of the serum acid phosphatase when either the alkaline enzyme level or the clinical picture suggests prostatic cancer. *Phosphorus* was estimated by the method of Fiske-Subbarow (17).

Cholesterol—The total serum cholesterol was determined by a method recently described by one of us (I.J.D.) (18), utilizing only 0.2 cc. of serum. The free fraction was estimated by a modification of the Schoenheimer-Sperry technic (19), and required 0.5 cc. The value for cholesterol esters was obtained by subtracting the figure for free cholesterol from that of the total.

Proteins—The estimation of total serum proteins and of the albumin fraction was performed according to the micro-Kjeldahl-direct-Nesslerization technique (10); the value for the globulin fraction was derived by subtraction. Non-protein-nitrogen controls were done by the micro-Kjeldahl method and colorimetric estimation according to the procedure of Wu (10). These methods were selected because the reagents are the same as those used for routine total non-protein-nitrogen determinations.

RESULTS

The results obtained in this series of cases are in the main detailed in Tables II and III. A better perspective can be gained and clearer comparisons made if the figures are considered under two main headings:

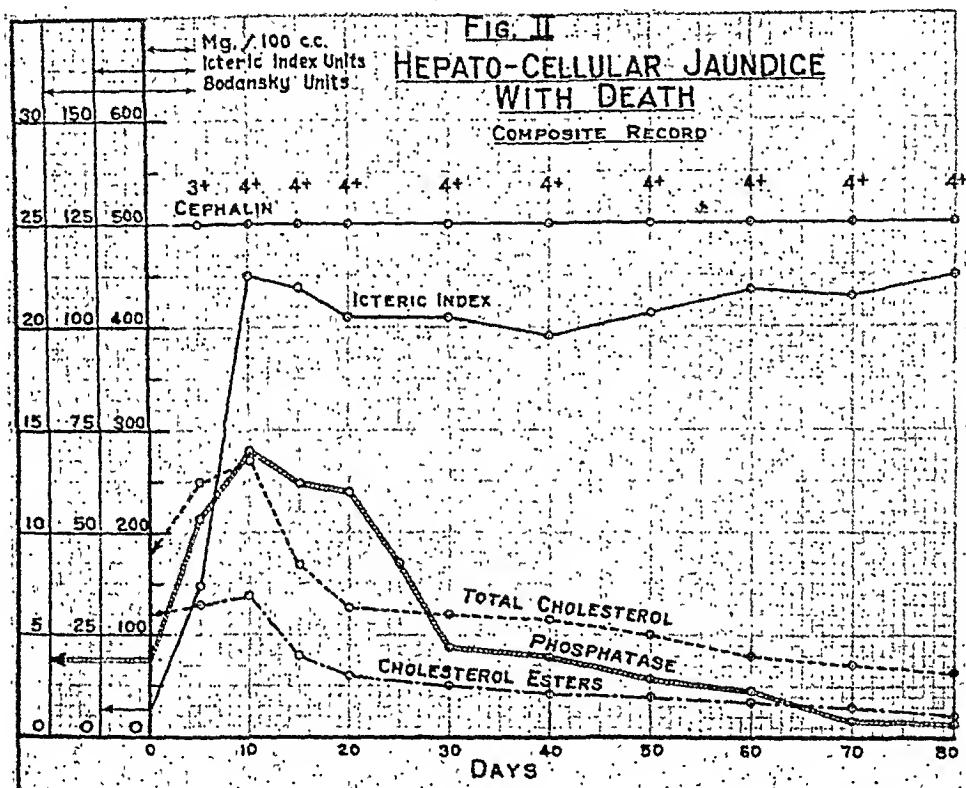
- I. Results of Individual Tests
- II. Composite Results in Typical Hepatic Syndromes

I. Results of Individual Tests

1. *Icteric Index.* The highest levels for bilirubin were reached in neoplastic obstruction. Values between 101 and 190 were found in 41% of the early* cases and 44% of the late* cases, and above 60 in 70%

passive hepatic congestion was associated with jaundice in only 18% of cases, and in the majority of these cases the icteric index remained below 20; occasionally, with concomitant pulmonary infarction, severer grades of jaundice were encountered.

2. *Van den Bergh (Direct).* Cirrhosis with jaundice produced a direct delayed Van den Bergh reaction in 75% of cases. The delayed reaction also predominated in the hepatocellular group, but to a lesser degree than in cirrhosis. A biphasic reaction occurred in 60-80% of all patients with obstructive jaundice, whether calculous or neoplastic in origin. Less frequently encountered was the direct immediate response; this was noted in 33% of late benign obstructions, 29%



and 79%, respectively. In the next highest group—late hepatocellular jaundice—there were only 6% with an index over 100, and only 44% over 60. The icteric index in both calculous obstruction and early parenchymatous jaundice ranged predominantly under 60, and in cirrhosis under 40, although in all three groups levels around 80 were occasionally reached.

In the hemolytic processes, the icteric index varied from 9 to 55, with a majority of the readings below 40; one exceptional case of sickle-cell anemia with severe hemolysis and canalicular thrombi reached the astounding figure of 250. In two hepatomas there was no jaundice. In two cholangiomas, with the tumor compressing the main ducts, the icteric index was 133 and 180, respectively; another cholangioma had an index of only 14. Right heart failure with chronic

of late neoplastic obstructions, and 16% of late hepatocellular jaundice—in each, usually associated with severe icterus.

Pure hemolytic processes caused a direct delayed reaction. The various types of infarction, usually accompanied by some hepatic pathology, generally had a biphasic Van den Bergh. Those cases of right heart failure associated with jaundice all had delayed responses.

3. *Cephalin-Cholesterol Flocculation.* Negative cephalin flocculation reactions were obtained most commonly in cirrhosis without jaundice (62%), in early calculous obstruction (91%), and in early neoplastic obstruction (93%). In the remaining 38% of non-jaundiced cirrhotics, from 1+ to 4+ reactions occurred, whereas in the remaining early obstructions there was rarely a response more severe than 1+.

* "Early" cases are arbitrarily defined as those in which the disease has been present for less than five weeks; "late" cases, those in which it has existed more than five weeks.

Conversely patients having cirrhosis with jaundice, hepatocellular jaundice (early and late), and late obstruction (both calculous and neoplastic) overwhelmingly exhibited 3+ and 4+ flocculations.

Gall-bladder disease without jaundice was associated with a negative cephalin reaction in 72% of cases; the rest had predominantly 1+ and 2+ reactions. Negative flocculation was also the rule in the hemolytic group. In passive congestion of the liver, although 60% were negative; it is noteworthy that 18% were associated with 3+ and 4+ responses, and 16% with 1+ and 2+; of these 34% positive reactors, only half were jaundiced.

Occasional 1+ and 2+ reactions (rarely 3+ or 4+) were obtained in malnutrition, diabetes mellitus, hyperthyroidism, hypothyroidism, metastases to the liver, lymphogranuloma venereum, lupus erythematosus disseminatus, pernicious anemia, multiple myeloma, and nephrosis, although as a rule there was no flocculation in these conditions. Hodgkin's disease and the leukemias, even when unassociated with jaundice, exhibited 3+ and 4+ reactions in half the cases.

4. Alkaline Phosphatase. As with the icteric index, the highest phosphatase levels were obtained in neoplastic obstruction. In 63% of early cases, the phosphatase ranged from 20 to 35 Bodansky units, and in 95% was over 12.1 units, while in late cases the value was above 20 and 12.1 units in 29% and 71%, respectively. Figures above 20 were obtained in two patients with hepatoma who had no jaundice.

Exclusive of the above, the highest values for phosphatase were found in early hepato-cellular jaundice and in early benign obstruction. An inverse relationship could be established between the phosphatase level and the duration of illness; thus the greatest incidence of subnormal figures was found in the group with late parenchymatosus jaundice (19%).

Predominantly normal values were present in cirrhosis, in the hemolytic group, and in the late benign obstructions. A tendency to moderate elevation of phosphatase levels was noted in malnutrition and in avitaminosis, especially when the subjects were alcoholics.

5. Total Cholesterol. By far the highest levels for total cholesterol were attained in neoplastic obstruction, especially when due to carcinoma of the head of the pancreas. Twenty-two percent of the patients observed in the early phases of this condition showed values ranging from 601 to 1210 mg.%¹, and an additional 59%, figures between 351 and 600 mg.%¹; in the late cases, such high values were less frequent. Moderate elevations were present in gall-bladder disease without jaundice and in the early stages of calculous obstruction, of parenchymatosus jaundice, and of cirrhosis. Total levels in late parenchymatosus jaundice were below 100 mg.% in 42% of cases, and below 150 mg.% in 75%.

Significant variations in cholesterol were observed in diseases not primarily associated with the hepatobiliary system. In approximately half the patients with cirrhosis, nephrosis, and hypothyroidism, levels above

200 mg.% were present. In frank myxedema, values as high as 750 mg.% were noted. In one case of xanthomatosis, a figure of 850 mg.% was reached. The total cholesterol was low in 54% of the patients with hyperthyroidism (between 100 and 150 mg.%), and in over one-third of those with malnutrition and avitaminosis (below 150 mg.%).

6. The Percentage of Esters in Total Cholesterol. A markedly subnormal percentage of cholesterol ester was found in the late phases of parenchymatosus and of obstructive jaundice. (They were below 50% of total in 83% and 79% respectively). Similarly, in 61% of cirrhotic patients with jaundice, esters represented less than 50% of the figure for total cholesterol. Lesser depressions were present in non-icteric cirrhotics and in subjects with right heart failure or mediastinal compression; in these, not only was the total incidence of subnormal values less, but also the occurrence of markedly low percentages of esters (below 40%) was relatively uncommon.

The majority of patients with gall-bladder disease and most of those with hemolytic jaundice exhibited a normal relationship between cholesterol esters and total cholesterol. In the patients having hyperthyroidism and malnutrition, there was a tendency for the ester percentage to be moderately subnormal.

7. Serum Proteins. Subnormal values for total serum proteins occurred in cirrhosis (40% of jaundiced and 52% of non-jaundiced patients), in hepatitis, and in the late phases of obstructive jaundice. It is exceptionally interesting that in two of these groups with predominantly low total proteins, there also occurred the greatest incidence of values *above* 8.6 Gm.%¹. We refer to cirrhosis with jaundice (13%), and late neoplastic obstruction (14%); in these same conditions was also found the greatest frequency of very low or reversed A/G ratios (58% and 57%, respectively).

Examination of individual case records revealed that many patients, while exhibiting normal or even high total protein levels, at the same time had definite hypoalbuminemia and hyperglobulinemia. Furthermore, many cases—even advanced chronic ones—had entirely normal figures for total proteins as well as for the component fractions.

In the non-hepatic group, abnormally high values were found for total proteins in roughly half the cases of multiple myeloma and hypothyroidism; the former were characterized by hyperglobulinemia, but the latter were usually unassociated with any disturbance of the A/G relationship. In six of eleven cases of nephrosis, the total serum protein concentration was below 5.9 Gm.%, and each was associated with a reversal of the A/G ratio. Values of 4.4-6.0 Gm.% were found in 35% of the malnutrition group, but here hypoalbuminemia and reversal of the A/G ratio occurred in only 21%.

H. Composite Results in Typical Hepatic Syndromes

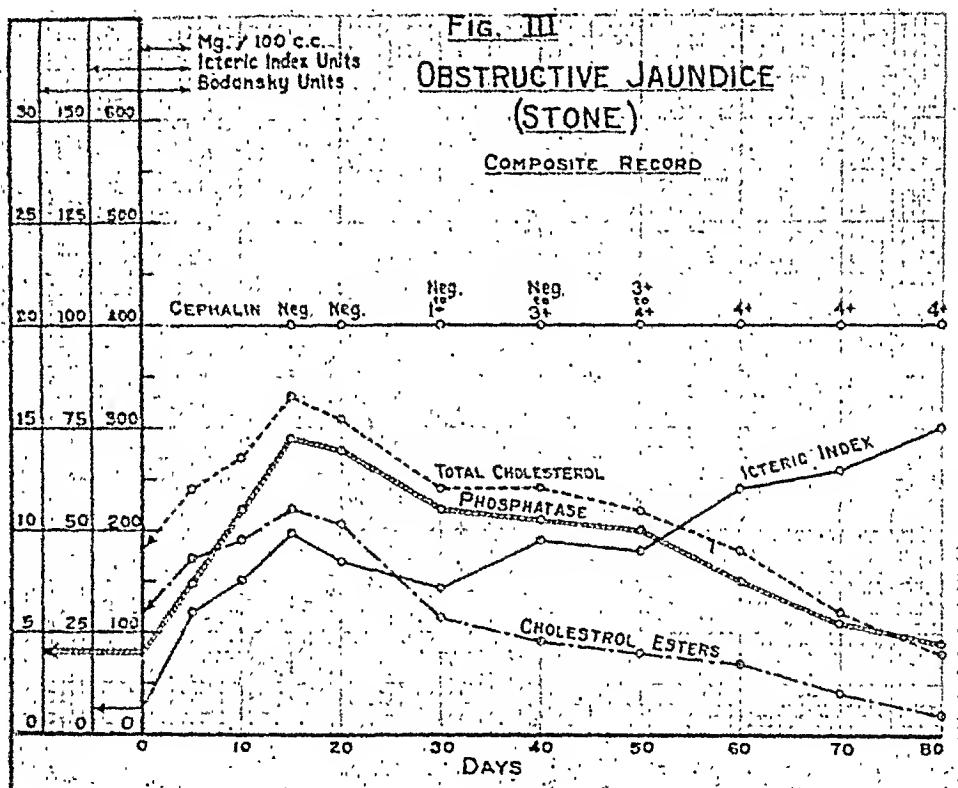
Individual analysis of any one of the above tests in relation to disturbances of the hepatobiliary system may be highly informative, but of itself does not afford any well-rounded concept of the status of the liver per-

A FASTING-BLOOD-SAMPLE PROCEDURE

any satisfactory approach to the differential diagnosis of the particular case with an alleged hepatic condition. The reasons for this may readily be appreciated: 1) No one procedure tests every function of the liver; 2) considerable overlapping of values from one hepatic syndrome to another is inevitable; and 3) non-hepatic disease frequently influences the result, as in the diabetic or the nephrotic.

Therefore, we must consider our group of tests as a unit. In this way, the simultaneous results obtained from all determinations fall into patterns, sufficiently clear and sharply demarcated to be of first hand importance in determining the diagnosis and in following the progress of the commonly encountered forms of

matory processes. There are some differences between the two. The *toxic* group is at times characterized by a relatively rapid development of intra-hepatic block, as mirrored by an early rise in the icteric index and in phosphatase and cholesterol values. The *inflammatory* group ("hepatitis," "catarrhal jaundice") more frequently exhibits early evidence of severe hepatic damage, as indicated by a sharp drop in the percentage of cholesterol esters and by a strongly positive cephalin flocculation. Where the process is primarily a *cholangitic* one, the characteristics of both these groups may be combined. However, except for the initial phases, all these types tend to follow the same pattern, and the individual variations will depend chiefly upon



hepato-biliary disease. With such treatment of our data, isolated, atypical deviations in the results of any single procedure lose their significance and cannot be misleading.

Thus it has seemed wise to correlate *all* the "composite-test" results as they occur simultaneously in each syndrome, and, still further, to demonstrate serial developments with all these tests over a period of time. To this end, we have constructed a number of graphs (Figs. I to IV) from our data, each illustrating the findings to be expected in a particular hepatic disturbance. The values for serum proteins have been omitted because of their great variability and therefore insignificant contribution to differential diagnosis.

1. *Hepato-Cellular Jaundice.* The term "hepato-cellular jaundice" is used broadly to indicate parenchymatous disease, and embraces both toxic and inflam-

the speed with which the process evolves.

Figure 1 affords a composite picture of a case of hepato-cellular jaundice with recovery. It can be seen that initially all values tend to rise as a result of intra-hepatic obstruction. As cellular damage progresses, the cephalin flocculation becomes markedly positive, and the percentage of esterified cholesterol falls (although the absolute value for esters remains as before, or even rises). When the damage becomes more severe, a striking fall in the percentage of esters occurs, followed shortly by a perceptible reduction of total cholesterol. At the same time, the phosphatase value falls, but not quite so quickly as the cholesterol.

This trend continues until the "critical phase"—in our cases, an average of three weeks—when signs of improvement are seen. The icteric index drops rapidly, and the phosphatase likewise falls, but much more

gradually. The total cholesterol and ester percentage begin to rise somewhat abruptly, with the former likely to reach temporary levels slightly above normal. The intensity of cephalin flocculation during this period gradually diminishes; in some instances it recedes *before*, and in others *after*, a progression towards normal in the results of other tests, but in the majority of instances moves concomitantly with them. Serum proteins are not characteristically altered at any stage of this condition. In the average case of the type depicted in Figure I, recovery may be expected within five or six weeks.

In those cases of hepato-cellular jaundice where improvement fails to occur (Figure II), serial determinations demonstrates a progressive, irreversible reduction in both the total and the esterified cholesterol to significantly low levels, with a constantly diminishing ester-total ratio. As the process continues and hepatic damage increases, the phosphatase falls—at first rapidly towards normal (even though intra-hepatic obstruction, as indicated by the high icteric index, persists), then more gradually to subnormal levels. During this whole period, the cephalin reaction usually remains 4+. The serum proteins, predominantly normal during the early phases, show a gradual drop, with hypoalbuminemia, hyperglobulinemia, and a tendency to a reversal of the A/G ratio as the patient becomes worse. The period of time from onset to death may vary from a few weeks to several months, and the speed with which the results of our tests change is predicted upon the rapidity with which death ensues.

2. Obstructive Jaundice Due to Calculus. When the common duct is blocked by stone, serial examinations with the "composite-test" yield a pattern of results different from that seen in hepato-cellular jaundice (Figure III). When the obstruction takes place, there is a uniform proportionate rise in the icteric index, phosphatase, total cholesterol, and cholesterol esters. The high levels for all these are maintained as the obstruction persists, and they fluctuate with the degree of obstruction. The percentage of cholesterol esters is well maintained for two to three weeks, and the cephalin reaction is either negative or only minimally positive for even longer periods of time. In comparison with parenchymatous jaundice, calculous obstruction generally has a lower icteric index. The phosphatase level, although perhaps lower than in early hepato-cellular jaundice, stays persistently elevated, whereas with hepato-cellular jaundice it invariably falls as the illness continues, and may ultimately reach subnormal levels.

A distinctive triad, then, for calculous obstruction includes: a normal percentage of cholesterol esters, a persistently negative cephalin reaction, and a continued moderate elevation of phosphatase.

If a diagnosis of benign obstruction is established and operation has relieved the block, all the figures return to normal quickly, sometimes in a matter of days. If the obstruction is not removed within three or four weeks, severe liver damage secondary to pressure (sometimes much earlier with superimposed cholangitis) becomes apparent, and a downhill course ensues

similar to that described under hepato-cellular jaundice. Strictures and inflammatory lesions blocking the common duct usually produce a picture comparable to that caused by stone.

3. Obstructive Jaundice Due to Neoplasm. The most common neoplasm producing obstructive jaundice is carcinoma of the head of the pancreas. However, other less frequently encountered neoplasms that have involved the common duct, either by local extension or by metastasis from more distant organs, cannot be distinguished by laboratory means. Apparently, the method of production of the jaundice is identical, particularly if we subscribe to Kaplan and Angrist's contention that jaundice with pancreatic carcinoma is caused by actual *invasion* of the common duct rather than by simple extrinsic pressure (20).

Neoplastic obstruction to the flow of bile into the duodenum presents a remarkably unique picture in the "composite-test," as can be visualized in Figure IV. As happens with benign obstruction, there is a progressive, concomitant rise of values for icteric index, phosphatase, total cholesterol, and cholesterol esters. Likewise the cephalin reaction remains negative and the percentage of esters is maintained at a high level for a relatively long time. In contrast to benign obstruction and parenchymatous jaundice, however, with this syndrome one sees unprecedentedly high values: in our cases, the icteric index ranged between 100 and 190 units; the total cholesterol, between 500 and 1200 mg.%; and the phosphatase, between 18 and 35 Bodansky units. What is more impressive, these elevations tend to persist for considerable periods of time. When obstruction has long been present, the first indication of liver damage is usually a reduction in the percentage of cholesterol esters. Then the cephalin reaction slowly becomes positive, the concentration of total cholesterol drops, and, finally, the value for phosphatase begins to fall. All this occurs in the face of a persistently deep icterus with a high index.

When the obstruction and jaundice are of somewhat intermittent nature—as is prone to occur in patients with ampullary carcinoma, and even in those with carcinoma of the head of the pancreas (21)—the test values will, of course, vary accordingly, but they will continue to reflect the balance existing between the parenchymal and the obstructive phases of the process.

Total and fractional protein levels are only moderately affected in the early stages of neoplastic obstruction. In view of the minimal cellular damage, this is to be expected. Such values become definitely abnormal when secondary parenchymal damage has occurred. Hypoalbuminemia and reversal of the A/G ratio follow a reduction in the percentage of cholesterol esters and an increase in the cephalin flocculation.

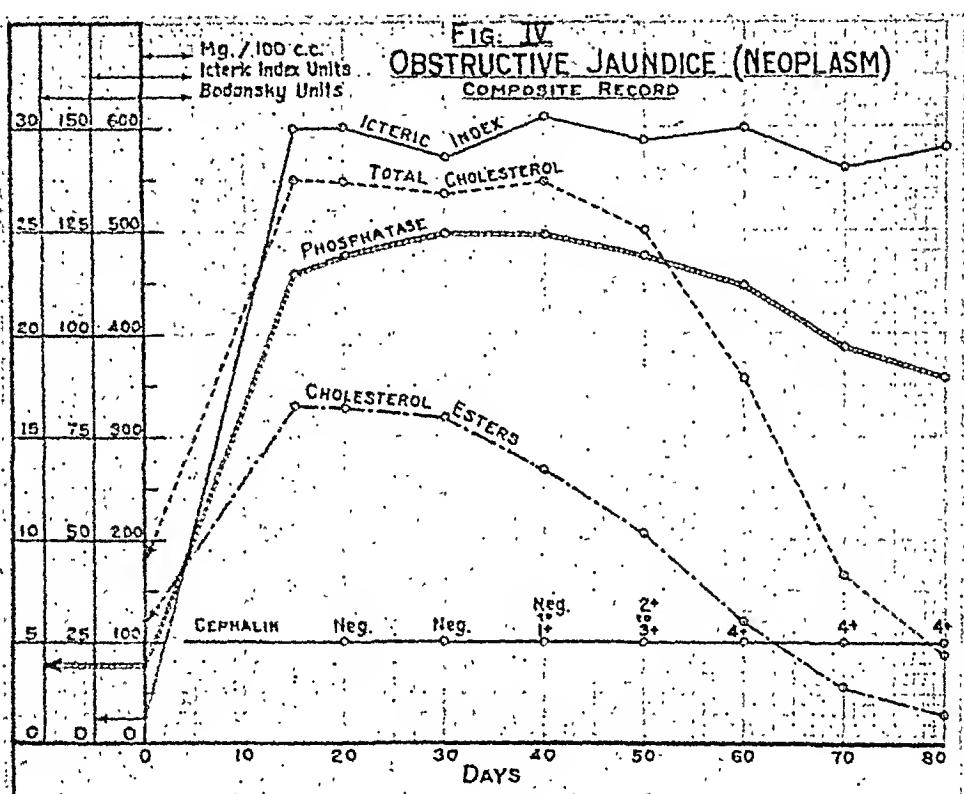
4. Cirrhosis and Fatty Degeneration of the Liver. It is practically impossible to make a diagnosis of cirrhosis of the liver on a purely laboratory basis. The recognition of this condition depends almost wholly on historical and clinical findings. The available "function" tests can merely indicate the presence of active

damage or a decrease in hepatic reserve. Thus, when the process is a chronic, slowly progressing one, all the laboratory findings may be within normal limits, or perhaps only the total proteins or the A/G ratio may be disturbed. However, when the process is an active one, as, for example, when jaundice is present, then one finds increasing evidence of cellular involvement, namely, a strongly positive cephalin, a low phosphatase, a low percentage of cholesterol esters, and a definite hypoalbuminemia and reversal of the A/G ratio.

By means of the "composite test" it is difficult to draw a sharp line between the cases of fatty degeneration of the liver and those of cirrhosis, especially since the two frequently co-exist. Acute fatty degeneration

sis, there is a shift to more abnormal figures. This may occur because of the precipitation of thrombi in the bile canaliculi, or because of the fever and metabolic disturbances prone to be associated with severe crises. In such instances, the findings of the "composite-test" will resemble those already described as a result of direct involvement of the hepatic parenchyma.

6. Chronic Passive Hepatic Congestion. This syndrome is most frequently seen in association with rheumatic heart conditions, cor pulmonale, and constrictive pericarditis, and to a lesser extent with the hypertensive and arteriosclerotic groups of cardiac disease. Jaundice is not common (found in only 18% of our cases), is usually not severe, and is always asso-



(or infiltration) exhibits a rapid clinical course, often characterized by marked hepatomegaly and ascites. The laboratory findings are similar to those in cirrhosis, but the incidence of indications of acute cellular damage is much greater.

5. Hemolytic Processes. Jaundice becomes apparent following hemolysis secondary to tissue infarction only if there is simultaneous derangement of hepatic function (22). Likewise, intravascular hemolysis, whether due to intrinsic systemic disease or to a toxic agent of exogenous origin, gives rise to jaundice more readily when the liver is already damaged, but the severity of the hemolytic process in such instances is an equally important factor, and may alone account for the icterus present. Moderate jaundice and a delayed or biphasic Van den Bergh reaction are the only positive findings in the average case. With unusual degrees of hemoly-

ciated with a delayed Van den Bergh reaction. The cephalin test, usually negative, may occasionally exhibit a 4+ flocculation in the presence of severe congestion. It is noteworthy that there is no correlation whatsoever between the presence or intensity of jaundice and the presence or intensity of cephalin flocculation. For instance, of our jaundiced cases, only half exhibited positive cephalin reactions, and of all the positive cephalin reactors, only a fourth were jaundiced.

The phosphatase and cholesterol values deviate little from the normal, with equal likelihood of moderately high or moderately low levels in a small number of cases. There is some tendency to low total protein and albumin concentrations, but there is no correlation between the low levels for total proteins and the reversal of the A/G ratio, either being likely to occur without the other. These variations are due, at least in part,

to various accompaniments of cardiac disease, such as anorexia, nausea, vomiting, and diarrhea.

7. *Gall-Bladder Disease Without Jaundice.* Abnormal findings with the "composite-test" in gall-bladder disease without jaundice are not so frequent as one might expect. Hypercholesterolemia, so often asserted to be common in cholecystitis and cholelithiasis, is

pect. The problem still remains one of the most difficult in the whole field of medicine. By virtue of the very incompleteness of our knowledge, there are two dangers: one, of making the subject hopelessly complex and confusing, the other, of oversimplifying it. A sensible approach requires that we carefully examine the available data, note any shortcomings, and then decide

TABLE I
Clinical Classification of Diseases Affecting the Hepato-Biliary System

	# Cases	% Total	# Cases	% Total
I. INTRA-HEPATIC PROCESSES			355	47.3
A. Hepato-cellular jaundice	108	14.4		
1. Infectious, inflammatory, bacterial, parasitic, viral, "catarrhal"	79	10.5%		
2. Toxic-heavy metals, sulfa drugs, cinchonines, benzols	29	3.9%		
3. Secondary to prolonged obstruction—see Group II				
B. Fatty degeneration	24	3.2		
C. Cirrhosis—portal, biliary, cardiac, hemochromatosis	154	20.5		
D. Neoplasms	69	9.2		
1. Primary—hepatoma, cholangionoma	4	0.53%		
2. Metastatic—from pancreas, lung, GI tract, prostate, ovary, breast	46	6.1%		
3. Systemic—Hodgkin's, sarcoma, lymphosarcoma, leukemia, myeloma	19	2.5%		
II. EXTRA-HEPATIC OBSTRUCTION			95	12.7
A. Congenital and acquired strictures of common duct	3	0.40		
B. Lithiasis and cholecystitis	51	6.80		
C. Neoplasms—pancreas, nodes, duodenum, ampulla, common duct, gall bladder	36	4.80		
D. Duodenitis?	5	0.66		
III. HEMOLYTIC PROCESSES			46	6.1
A. Hemolytic anemias	6	0.80		
—congenital, acquired, sickle-cell				
B. Transfusion incompatibilities	7	0.93		
C. Infarctions—pulmonary, myocardial, splenic, mesenteric	33	4.40		
IV. MISCELLANEOUS DISEASES			254	35.9
A. Right heart failure	50	6.66		
B. Hypo-, hyperthyroidism	34	4.53		
C. Diabetes mellitus	45	6.00		
D. Lipoïd dystrophies	2	0.26		
E. Nephrosis	11	1.46		
F. Amyloidosis	4	0.53		
G. Acitominoisis and malnutrition	28	3.72		
H. Pernicious anemia, polycythemia	11	1.46		
I. Ulcerative colitis	6	0.80		
J. Pituitary, adrenal, genital disorders	25	3.33		
K. Bleeding peptic ulcer	13	1.73		
L. Others	25	3.33		
TOTAL CASES			750	100%

present in only one-third of our cases; in fact, a fifth of our cases exhibit subnormal values for total cholesterol, with some tendency to a moderate reduction in the percentage of esters. The cephalin flocculation is moderately positive in a few instances, and an elevation of phosphatase is occasionally present. The values for proteins deviate from the normal in a small number of instances.

DISCUSSION

There is no *open sesame* to the diagnosis and management of hepatic disease, and there is none in prospect which can be of real, practical use.

Several tests simultaneously performed in relatively large series of cases have been subjected to critical analysis and comparison under well controlled conditions by competent workers. We refer to the results obtained by the use of the cephalin-cholesterol flocculation procedure, both intravenous and oral hippuric acid tests, varied types of bromsulphalein retention studies, and the colloidal gold reaction (23), (24) (25). Further work along these lines is needed.

In selecting procedures for inclusion in the "composite-test" group, it was necessary to perform in parallel some of the better known of these individual tests, such

as the rose Bengal and bromsulphalein retention, hippuric acid formation, galactose tolerance, prothrombin indices, and the Takata-Ara reaction. It would carry us far afield at this point to attempt a correlation of our data in regard to these, to say nothing of reviewing a vast literature on the subject. Interesting comparisons are however, afforded within the scope of the selected tests themselves, and we shall confine ourselves mainly to these.

We have found the cholesterol ester ratio and total

the cephalin flocculation reaction to be the most sensitive indices of intra-hepatic disturbance, the percentage of esters being the more reliable of the two. With severe hepatic damage, both tests have given unequivocally positive results. However, with lesser grades of hepatic impairment—as in very early hepatocellular jaundice, cirrhosis, and chronic passive congestion of the liver—a reduction in the percentage of cholesterol esters usually preceded the appearance of a positive cephalin flocculation. In progressive obstructive jaundice, with beginning secondary hepatic involvement, lowered ester ratios were commonly found while the cephalin reaction was still negative. Of all types and stages of hepatic involvement, one-fifth of the cases with a low percentage of esters were associated with negative cephalin reactions. Conversely, it was uncommon to find a patient with a positive flocculation test with a normal percentage of esters when there was clinical or other laboratory evidence of hepatic impairment.

It is difficult to attach any significance to a positive cephalin flocculation in cases where there is no apparent clinical disease, or where the disease process appears to be remote from the liver and no other indication of hepatic impairment is obtainable on exhaustive investigation. Controversial reports have appeared concerning "false-positive" reactions. Their interpretation has assumed particular importance now in war industries, where hepatic pathology is prone to develop on contact with various chemical agents. Here the easily performed cephalin reaction is widely used to test prospective employees for existing liver disease, and a positive flocculation has been deemed cause for non-employment. With the current man-power shortage, avoidance of unnecessary rejections because of false positive tests is clearly desirable; furthermore, the patient ought not to be unjustly or unnecessarily stigmatized.

Among the possible causes of hitherto unexplained positive flocculations, the following deserve consideration:

1. The patient may really have hepatic impairment. If this is so, it should be susceptible to confirmation by other tests. The degree of involvement may be so minor as to be detectible only by the more sensitive procedures.

2. The technic of collecting the blood or of performing the test may be faulty. The specimen may have been hemolyzed, contaminated, or exposed to undue heat, or the reagents used in its performance may have deteriorated. (See Methods).

3. There may be undiscovered changes in the serum globulins (from fever, toxins, etc.) which are responsible for the flocculation, and in no way involve the integrity of the hepatic cell.

At one point we considered that thiamin deficiency might possibly be one of the causes of positive flocculation. However, in a number of patients purposefully kept on thiamin deficient diets* for weeks, previously positive cephalin reactions returned to normal as rapidly as in those with a full vitamin supplement.

Recently we noted a large number of unexpected positive cephalin reactions, some of them in patients in whom we had previously observed no flocculation. Investigation revealed that our usual stock of cholesterol had been exhausted, and temporarily several other commercial brands had been substituted for it. When several weeks later, we returned to the use of the brand previously employed,** the incidence of false positive reactions decreased.

In spite of technical precautions, we, too, have encountered a fair number of positive reactions in a heterogeneous group of patients who had no other evidence of hepatic derangement. In such cases we have been inclined to disregard 1+ and 2+ flocculations as significant of hepatic pathology.

Probably of least diagnostic value were the studies of blood proteins. There was a great tendency to variation in different diseases, in any given disease, and even in a single patient from time to time. The concentration of total proteins was especially subject to inexplicable alterations. However, it was significantly raised in multiple myeloma and myxedema, and lowered in nephrosis, and thus was of suggestive value in diagnosis.

The individual values for albumin and globulin and for the A'G ratio were useful in prognosis and in evaluating the results of therapy. They bore no recognizable relationship to the results of any of the other tests at any given time. Moreover, variations in them did not reflect changes in the severity of a morbid process either as accurately or as promptly as did the results of some of the other determinations routinely made.

The icteric index, phosphatase, and total cholesterol levels could be concomitantly and uniformly correlated in purely obstructive icterus, but only in the phase of rising jaundice. When the obstruction was either partially or completely relieved, the icteric index fell much more rapidly than did the other two, so that the patient might be practically free of jaundice though phosphatase and cholesterol values were still high. We believe this situation occurred because the crystalloid or "unbound" bilirubin is excreted easily through the kidney.

On the other hand, when the obstruction persisted and secondary parenchymal damage supervened, the levels of these three tests began to diverge, with the phosphatase and cholesterol falling even though the icteric index remained elevated. In these instances, too, an immediate or delayed Van den Bergh reaction usually changed to a biphasic one.

* Unpublished data.

** Manufactured by the American Cholesterol Products Company, Inc., Milltown, N. J.

TABLE II
*Range of Values in Classical Types of Hepatic Dysfunction
With Percentage Distribution of Cases**

	# cases	ICTERIC INDEX								VAN DEN BERGH DIRECT				CEPHALIN				PHOSPHATASE							
		3 - 8. Units								Negative				Negative				2.0-5.5 Bodansky U. Children: 3.0-15.0							
Normal response	100	8 20	21 40	41 60	61 80	81 100	101 150	151 190	Neg. Neg.	Del. ---	Biph. ---	Immed. ---	Neg. Neg.	1+ 1+	2+ 2+	3+ 4+	4+ 4+	0.9- 2.0	2.1- 5.5	5.6- 9.0	9.1- 12.0	12.1- 20.0	20.1- 35.0	60- 100	
Cirrhosis without jaundice	90	100	62	11	9	6	12	...	82	9	10	21	
Cirrhosis with jaundice	64	51	22	9	18	73	18	9	16	7	8	18	51	5	47	28	14	6	...	7		
Hepatitis, Hepato-cellular	Early	77	26	30	22	19	3	...	8	48	37	7	4	7	15	15	59	...	19	25	58	18	...	11	
	Late	31	19	18	19	20	18	6	...	18	34	32	16	3	3	10	16	68	19	30	26	19	...	42	
Obstructive jaundice (stone)	Early	45	38	29	12	21	29	60	11	21	7	2	26	38	24	12	
	Late	61	...	33	33	33	62	33	17	50	33	...	50	33	17	17	
Obstructive jaundice (neoplasm)	Early	22	...	9	14	14	13	86	15	...	86	14	93	7	5	32	53	
	Late	14	...	7	14	6	29	22	22	...	71	29	14	...	29	22	35	...	7	...	22	42	29	7	
Hemolytic processes	46	54	28	18	33	67	...	81	13	6	76	24	
Chronic passive congestive of liver	50	12	4	2	82	18	56	6	10	4	14	4	52	28	4	2	
Right heart failure																									
Gall-bladder disease without jaundice	23	70	13	13	4	...	9	57	34	

* Boxed numbers show predominant range in each group.

Our combination of tests, used as a unit, compared very favorably with the other "liver function" tests that were frequently performed in parallel. In our hands, the "composite-test" was generally much more reliable for differential diagnosis and for indicating the progress of disease than were the 2 mg. bromsulphalein, the oral galactose tolerance, and the oral hippuric acid tests, and about equal to these in estimating hepatic reserve. The Weltmann reaction usually paralleled the rate of erythrocyte sedimentation in "active" processes (whether hepatic or not), but was not very sensitive where fibrotic changes predominated. The Takata-Ara reaction, dependent primarily upon alterations in albumin and globulin, was in no way specific for cirrhosis; we found positive responses in patients with no cirrhosis, and negative ones in those with proven cirrhosis. Duodenal drainage was occasionally useful diagnostically and therapeutically. However, it

is extremely time-consuming for the physician and frequently most formidable for the patient.

A simple test, and one which proved to be of great aid in following the course of obstructive jaundice, was urinary concentration of bile and urobilinogen. Daily determinations gave a continuous picture of the presence or degree of obstruction, and, when used in conjunction with the "composite-test," aided in establishing or corroborating the diagnosis.

Abnormally decreased prothrombin levels invariably indicated a hemorrhagic tendency. The test, *per se*, afforded us no means of distinguishing a disturbed intra-hepatic synthesis of prothrombin and a delayed intestinal absorption of the fat-soluble vitamin K. For the most part, we were unable to confirm the value of the vitamin K test for differentiating hepatic and obstructive jaundice proposed by Lord and Andrus (26) and by Kark and Sonter (27); contrary to their ob-

TOTAL CHOLESTEROL				% CHOLESTEROL ESTERS				TOTAL SERUM PROTEINS					ALBUMIN				GLOBULIN				A/G RATIO						
150 - 200 mgm. %				65 - 75%				6.5 - 8.5 gm. %					4.5 - 6.0 gm. %				1.5 - 3.0				1.5 - 3.5 gm. %						
101	141	201	351	601	12-	36-	51-	66-	4.1-	5.6-	6.6-	7.6-	8.6-	1.4-	2.6-	3.6-	4.6-	1.1-	2.6-	3.6-	4.6-	2.2-	1.1-	1.6-	2.1-	2.9-	
150	200	350	600	1210	35	50	65	75	5.5	6.5	7.5	8.5	10.3	2.5	3.5	4.5	6.1	2.5	3.5	4.5	6.2	1.0	1.5	2.0	2.8	4.0	
25	29	25	—	—	1	15	36	48	5	47	42	5	1	14	41	26	19	29	32	25	9	29	35	26	10	...	
22	13	58	—	—	19	42	23	16	6	34	31	16	13	29	31	14	26	5	31	31	33	58	29	7	6	...	
22	28	17	22	—	14	31	52	13	11	18	36	28	7	7	25	39	29	17	29	37	17	42	26	22	7	3	
33	13	9	3	—	32	51	10	7	9	32	33	19	7	17	44	32	7	3	29	29	39	58	29	10	3	...	
9	36	55	—	—	—	—	58	42	—	2	55	36	7	—	15	49	36	15	55	25	5	2	27	60	11	...	
17	33	33	—	—	50	33	17	—	—	50	33	17	—	17	66	17	—	17	66	17	—	33	33	33	—	...	
—	5	14	59	23	—	41	54	5	5	27	52	27	9	14	22	47	17	27	46	18	9	23	31	28	18	...	
29	14	14	29	7	29	50	21	—	—	29	56	21	14	36	50	14	—	14	36	21	29	57	36	7	—	...	
15	72	13	—	—	—	4	11	85	6	22	59	13	—	4	27	60	9	17	43	24	16	20	41	26	13	—	
22	63	16	—	—	—	10	32	50	10	18	46	22	4	10	28	44	18	28	38	22	12	30	38	18	10	4	
22	43	35	—	—	—	—	—	30	70	4	21	50	21	4	—	22	43	35	35	56	9	—	4	52	22	13	9

servations, many of our patients with definite intrahepatic disease exhibited prompt increases in prothrombin levels on parenteral injection of vitamin K. It may be said that the prognosis was poor if the prothrombin concentrations remained persistently low despite the repeated parenteral administration of vitamin K. Of distinct bearing on the value of prothrombin estimation was the interesting observation that low values were often present in our patients with no hepato-biliary disease who were receiving sulfonamide therapy. This was perhaps dependent upon decreased bacterial activity in the intestine, with resultant interference in the synthesis of vitamin K.

It should be emphasized that single tests of "liver function" are generally of very limited usefulness. The range of values for a single test is so broad that results in one hepatic syndrome are readily confused with those in several others. For instance, the test may be

negative in the face of actual hepatic pathology; it may be overly sensitive and give false positive reactions; or it may be influenced by conditions entirely outside the liver. The common practice of employing a single test represents a form of false economy, since so little real information—and too often *wrong* information—is obtained. Of obviously greater value is the use of a selected group of tests, some of greater sensitivity and some of lesser, each of which serves to check the others, thus eliminating many errors. The simultaneous use of such a group, particularly when serially repeated, offers a much clearer overall picture in any given case. Of course, laboratory findings must always be interpreted in conjunction with the clinical findings. The clinical acumen of one physician may be naturally better than that of another; judicious utilization of laboratory procedures will help both.

Our selection of tests is in no way exclusive, and it

may not even be the optimum. However, the performance of these procedures is relatively simple and, at least in our hands, very likely to afford a comprehensive picture of any hepato-biliary condition which may exist. If the "composite-test" does not supply the required information, it usually indicates the other pro-

2. Results of the "composite-test" in 750 patients, performed more than 1400 times, are detailed.

3. Conditions in which the test were carried out have been grouped into intra-hepatic processes, comprising 47.3 per cent of the total; extra-hepatic obstructions, 12.7 per cent; hemolytic processes, 6.1 per cent;

TABLE III
Miscellaneous Conditions Affecting the Liver

Disease	Significant Deviations in Results of the "Composite Test"					
	Cephalin	Phosphatase	Total cholesterol	Cholesterol ester	Total serum protein	A/G ratio
Diabetes mellitus	Occasionally 1+, 2+		200-400 mgm. % in 55% of cases			
Hyperthyroidism	Occasionally 1+, 2+		100-150 mgm. % in 54% of cases			
Hypothyroidism	Occasionally 1+		200-750 mgm. % in 61% of cases	Normal to moderately subnormal	Over 8.5 gm. % in 42% of cases	
Malnutrition, Avitaminosis	Occasionally 1+, 2+; rarely 3+, 4+	5.6 to 9.0 units in 16% of cases	Below 150 mgm. % in 36% of cases	51 to 65% in 35% of cases	4.4 to 6.0 gm. % in 35% of cases	A/G reversal in 21% of cases
Nephrosis	Occasionally 1+		200-450 mgm. % in 45% of cases		Below 5.0 gm. % in 55% of cases	A/G reversal in 55% of cases
Ulcerative colitis					5.6 to 6.5 gm. % in 34% of cases	A/G reversal in 34% of cases
Bleeding peptic ulcer					Occasionally low	
Multiple myeloma	Occasionally 1+				Over 8.5 gm. % in 50% of cases	Hyperglobulinemia with low A/G in 50% of cases
Metastases to liver; Hodgkin's; Sarcomas; Leukemias		May vary from normal to picture of A) Hepato-cellular jaundice, or (B) Obstructive jaundice. Data obtained depend on site and diffuseness of involvement.				

cedures that may be most fruitfully employed.

In regard to functional tests of the liver, we thoroughly believe, with Ivy and Roth (28), that learning to interpret one set of tests well is better than a casual understanding of many procedures. As a result of extensive study, we feel that the "composite-test" affords a maximum of aid in diagnosis, prognosis, and therapy, and a minimum of discomfort to the patient.

SUMMARY

1. A single-venous-blood-specimen procedure (the "composite-test") for the appraisal of liver function is described. Simultaneous determinations have been made of the icteric index, Van den Bergh reaction, the cephalin-cholesterol flocculation, phosphatase, total cholesterol, cholesterol esters, total proteins, albumin, and globulin. Modifications in standard procedures for the performing of these tests were made whenever necessary in the interests of economy and simplicity, whenever and wherever accuracy was not sacrificed; in some instances, errors were reduced or eliminated.

and miscellaneous diseases, 33.9 per cent. Diagnoses were confirmed by clinical findings and course, roentgen-ray examinations, peritoneoscopy, biopsy, operation, and autopsy.

4. The data obtained from each individual test have been separately summarized and analyzed in relation to the existing disease state.

5. As a result of serial examinations, a pattern of results to be expected in each of the following syndromes involving hepatic dysfunction has been reconstructed: hepato-cellular jaundice; obstructive jaundice due to calculus; obstructive jaundice due to neoplasm; cirrhosis and fatty degeneration of the liver; hemolytic processes; chronic passive congestion; gall-bladder disease without jaundice.

6. The "composite-test" appears to yield results which are as delicate, as accurate, and as informative as those deriving from the use of the more elaborate individual tests. Comparisons are made with the results of other tests.

REFERENCES

1. Klotz, S. D.: An Analysis of Liver Functions by a Simplified Combination of Laboratory Tests, Bull. New York M. College, Flower & Fifth Ave. Hosps. 6:1-23, (April) 1943.
2. Mann, F. C., in Discussion of Papers on Liver Function, Am. J. Digest. Dis. 9:25-26, (January) 1942.
3. Steigmann, F., Popper, H., and Meyer, K. A.: Liver Function Tests in Clinical Medicine, J.A.M.A. 122:279-285 (May, 29) 1943.
4. Lichtman, S. S.: Diseases of the Liver, Gallbladder and Bile Ducts, Philadelphia, Lea & Febiger, 1942.
5. Duncan, G. G.: Diseases of Metabolism, Philadelphia, W. B. Saunders Co., 1942.
6. Bodansky, A.: Non-osseous Origins of Serum Phosphatase, Proc. Soc. Exper. Biol. & Med. 42:800-804 (December) 1939.
7. Sharnoff, J. G., Lisa, J. R., and Riedel, P. A.: Serum Phosphatase Activity in Disease of the Liver: Correlation of the Serum Enzyme Activity and the Hepatic Histologic Changes, Arch. Path. 33:460-466 (April) 1942.
8. Steigmann, F., and Popper, H.: Intrahepatic Obstructive Jaundice, Gastroenterology 1:645-654 (July) 1943.
9. Elias, H., and Schwimmer, D.: To be published.
10. Chaikin, N. W., and Schwimmer, D.: Hepatitis in the Course of Brucella Infection: Report of a Case, Rev. Gastroenterol. 10:130-132 (March-April) 1943.
11. Meulengracht, E.: Blood Sugar Curve in Various Forms of Icterus, Acta med. Scandinav. 79:32-75, 1932.
12. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. 2, Baltimore, Williams & Wilkins, 1932.
13. Hanger, F. M.: The Flocculation of Cephalin-Cholesterol Emulsions by Pathological Serums, Tr. A. Am. Physicians 53:148-151, 1938.
14. Thudiehum, J. L. W.: A Treatise on the Chemical Constitution of the Brain, London, Bailliere, Tindall & Cox, 1884.
15. Pohle, F. J., and Stewart, J. K.: The Cephalin-Cholesterol Flocculation Test as an Aid in the Diagnosis of Hepatic Disorders, J. Clin. Investigation 20:241-247 (March) 1941.
16. Bodansky, A.: Phosphatase Studies. II. Determination of Serum Phosphatase. Factors Influencing the Accuracy of the Determination, J. Biol. Chem. 101:93-194 (June) 1933.
17. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. 66:375-400 (December) 1925.
18. Drektor, I. J.: A New Method for the Direct Determination of Cholesterol, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. 6:138-141 (October) 1943.
19. Shoenheimer, R., and Sperry, W. M.: A Micromethod for the Determination of Free and Combined Cholesterol, J. Biol. Chem. 106:745-760 (September) 1934.
20. Kaplan, N., and Angrist, A.: The Mechanism of Jaundice in Cancer of the Pancreas, Surg., Gynec. & Obst. 77:199-204 (August) 1943.
21. Berk, J. E.: Diagnosis of Carcinoma of the Pancreas, Arch. Int. Med. 68:525-559 (September) 1941.
22. Rich, A. R.: The Pathogenesis of the Forms of Jaundice, Bull. Johns Hopkins Hosp. 47:338-377 (December) 1930.
23. Mateer, J. G., Baltz, J. I., Marion, D. F., Hollands, R. A., and Yagle, E. M.: A Comparative Evaluation of the Newer Liver Function Tests, Am. J. Digest. Dis. 9:13-25 (January) 1942.
24. Mateer, J. G., Baltz, J. E., Marion, D. F., and MacMillan, J. M.: Liver Function Tests, J. A. M. A. 121:723-728 (March 6) 1943.
25. Gray, S. J.: The Colloidal Gold Reaction of Blood Serum in Diseases of the Liver, Arch. Int. Med. 65:524-544 (March) 1940.
26. Lord, J. W., Jr., and Andrus, W. DeW.: Differentiation of Intrahepatic and Extrahepatic Jaundice, Arch. Int. Med. 68:199-210 (August) 1941.
27. Karle, R., and Souter, A. W.: The Response to Vitamin K: A Liver-Function Test, Lancet 2:693-695 (December 6) 1941.
28. Ivy, A. C., and Roth, J. A.: Why do a Liver Function Test? Gastroenterology 1:655-668 (July) 1943.

Hydrochloric Acid Therapy in Achlorhydria

By

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MOST medical textbooks advise the administration of dilute hydrochloric acid in cases of achlorhydria. The dose usually recommended is 2 to 4 c.cm. of dilute HCl (B.P.) to be taken in 4 to 8 ounces of water during a meal. Several investigators have demonstrated the failure of the usual therapeutic doses of dilute HCl to increase intragastric acidity in achlorhydria.

Hurst (1923) recognised the inadequacy of the official pharmacopoeial dose of HCl and advocated quantities of 4 to 6 c.cm. which many considered to be a radical recommendation. Kern, Rose and Austin (1926) investigated the effect of orally administered HCl upon gastric contents in normal individuals and in patients with achlorhydria, and they agreed with Hurst. Shay and Gershon-Cohen (1936) working on a comparison of the effectiveness of glutamic acid hy-

drochloride and dilute HCl as the replacement therapy in anacidity, measured by fractional gastric acid titration and hydrogen-ion concentration curves, showed that 7.5 to 10 c.cm. of dilute HCl added to the Ewald test meal produced a low free acid curve during fractional analysis, while 5 c.cm. were inadequate to show any free acid. Crohn (1918) in his studies on fractional estimation of the stomach contents and the effects of HCl therapy on the acid titre of the stomach during digestion in achlorhydric patients obtained the same results. He found that small doses of acid administered to the fasting stomach disappeared promptly, the last trace leaving within 25 minutes. Therapeutic administration of acid with a test meal was of advantage only for the first half hour and the increase of the acid titre was very moderate. The best results were obtained when small doses of acid were given every 15 minutes during digestion, but this method is hardly practical for everyday use.

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I have repeated some of Crohn's work. Ten patients with a histamine-fast achlorhydria were given 560 c.cm. of the Rehfuss test meal, to which 4 c.cm. of dilute HCl were added. Specimens were withdrawn every 15 minutes for 90 minutes and an analysis made of each specimen. The results obtained concur with the conclusions reached by him. Eight patients showed complete achlorhydria in all specimens. Only two patients showed a slight rise of free acidity from 5 to 8 c.cm. N/10 during the first hour of the test.

The HCl-combining power of various cooked staple foods was next investigated. As acid is usually administered during a meal, this *in vitro* investigation was thought to throw some light on the complex processes occurring in the stomach during digestion. 50 grammes of dehydrated food were finely minced and to it was added 10 c.cm. of dilute HCl (B.P.) and 90 c.cm. of water. Each 10 c.cm. of this acid solution contains 0.1 gramme of acid. The mixture was incubated at 37°C for 2½ hours. It was then filtered and 10 c.cm. of filtrate, to which 1 drop of Toepfer's indicator was added, were titrated against N/10 solution of NaOH. The remaining free and total acidities were determined and the combining power of 100 grammes of food with HCl was calculated in terms of grammes of HCl.

The first group of dehydrated food substances tested contained proteins and included beef, lamb, cod and liver. The results of the titrations show that 100 grammes of these articles will neutralise from 1.2 to 1.6 grammes of HCl, equivalent to 12 to 16 c.cm. of HCl dil. (B.P.). The remaining total acidity is high owing to the formation of acid proteins. The second group of food substances which was tested contained carbohydrates including potato, cabbage, carrot, pastry, toast and sausage meat. In this group from 0.4 to 0.8 grammes of free HCl or 4 to 8 c.cm. of HCl dil. (B.P.) were found to be neutralised by 100 grammes of dehydrated food. The remaining total acidity was only slightly above the free acidity in the titrations of these food substances. Again, 100 c.cm. of milk was found to neutralise 3.3 c.cm. of HCl (B.P.).

It can thus be seen that various articles of food have a considerable combining-power with HCl and play a part in reducing gastric acidity, a fact which can be utilised in the treatment of peptic ulcer.

The neutralising power of the Rehfuss test meal was also estimated. The meal is made by boiling two tablespoonsful of fine breakfast oatmeal in a quart of water until the total bulk is reduced to one pint. Two tablespoonsfuls of fine oatmeal weighed 55 grammes. A known amount of acid was added to the prepared test meal and titrated against N/10 NaOH and it was found that this test meal neutralised 0.33 gramme of HCl or 3.3 c.cm. of HCl dil. (B.P.). The readings for free HCl in a fractional gastric analysis are therefore influenced by the amount of gruel in the test meal. This neutralising power of the gruel explains the achlorhydric and low acidity curves obtained by fractional gastric analysis on achlorhydric patients who had taken

gruel meals to which varied amounts of acid were added. The amount of oatmeal commonly used is two tablespoonsful. This measure is open to a variable interpretation. In addition, the same measure of different varieties of oatmeal varies in weight. Thus, two tablespoonsful of a coarse oatmeal weighed 67 grammes and would neutralise more acid. It is therefore suggested that a standard weight of oatmeal should be employed for the preparation of the test meal, and 2 ounces were found to be a satisfactory amount.

Table 1

Food (50 gm.)	Remaining free acidity in 10cc. of filtrate (cc. —————— N NaOH.)	Total acidity in 10cc. N NaOH.)	Combining power of 100 gm. of food with HCl in gramme.	Equivalent amount of HCl in cc. of HCl dil. (B.P.)
Beef	6	12	1.56	15.6
Lamb	5	12	1.62	16.2
Liver	10	15	1.26	12.6
Cod	5.4	10.8	1.60	16
Potato	20.5	22.5	.51	5.1
Cabbage	17	19	.76	7.6
Pastry	16	19	.82	8.2
Carrot	17.1	18.9	.74	7.4
Sausage meat	17.6	20.4	.72	7.2
Toast	22.7	23.3	.34	3.4
Milk (90 cc.)	18.5	25.5	.33	3.3
			(100 cc.)	

The fasting juice was examined in seven achlorhydric patients. To 9 c.cm. of fasting juice 1 c.cm. of dilute acid was added and the remaining free acidity was obtained by titrating against N/10 NaOH. The neutralising power of fasting juice was then calculated and it was shown that 50 c.cm. of fasting juice neutralised from 0.022 to 0.061 gramme of acid or 0.22 c.cm. to 0.61 c.cm. of HCl dil.

Different dilutions of acid in water were tested to see how much acid could be conveniently given in one dose during a meal. The various solutions were sweetened with sugar and flavoured with tincture of orange to make them as palatable as possible. 4 c.cm. of HCl dil. (B.P.) in 4 ounces of water was found to be too strong and could not be taken comfortably, but 6 c.cm. in 8 ounces of water was more easily tolerated. This dose is inadequate to raise appreciably the presence of free acid in the stomach during the digestive cycle after a good meal in achlorhydric patients, though it may have some beneficial effect when given during a small meal or to patients who are still capable of producing some free acid themselves. That this is so was proved by asking six patients with achlorhydria to drink 6 c.cm. of HCl (B.P.) in 8 ounces of water with their meal. 15 c.cm. of stomach contents were aspirated every 15 minutes during 90 minutes after the meal. No free HCl was found in the stomach contents after the meal.

DISCUSSION

The fasting normal stomach secretes gastric juice continuously at a rate varying between 10 and 60 c.c.m. per hour. The resting contents are on an average about 30 c.c.m. and free HC1 is present. 500 c.c.m. or more of gastric juice are secreted after a good meal and the juice probably contains 0.5 to 0.6 per cent of HC1, but the acidity is reduced by neutralisation to the levels usually observed in test meals. The normal average volume of free acid after a histamine test meal per hour is 182 c.c.m. N/10 HC1, which is equal to 0.664 gramme of HC1. If secretion continues at this rate about 2 grammes of HC1 are therefore secreted in three hours. Ingestion of food lowers the free acidity considerably by neutralisation and dilution of gastric juice. Swallowed saliva, the alkaline pyloric secretion, and mucus which is present in gastric secretion, in addition to regurgitation of the alkaline juices from the duodenum, lower the free acidity still further. The free acidity at any time depends on these various processes and rarely rises above 0.15 to 0.2 gramme per cent of HC1. That this free acid level should be maintained in the stomach is desirable as the acid has a number of important digestive functions, and replacement therapy is indicated if it can be carried out successfully. As 1 c.c.m. of dilute HC1 (B.P.) contains 0.1 gramme of the acid, between 15 and 20 c.c.m. of the pharmacopoeial preparation should be required with a good meal to keep the free acidity at normal levels. Such a dose cannot be tolerated. The experiments showed that various foodstuffs have a strong neutralising and binding power for the acid, and that

even the resting juice in histamine-fast achlorhydric patients binds a certain amount of HC1. From these considerations the calculated amount of acid required does not appear to be exaggerated.

Clinically, spectacular therapeutic results are sometimes obtained with HC1 for the relief of vague, but distressing digestive symptoms, allergic conditions, or in gastogenous diarrhoea in achlorhydric patients. These effects derived from HC1 in the usual dosage cannot be caused by the presence in the stomach of any free acid at the time of digestion. Whether the effects are psychological, or are due to some acid reaching the duodenum and stimulating it to secrete its vital hormones, remains a matter of conjecture.

SUMMARY

It has been known that the administration of dilute HC1 to achlorhydric patients in therapeutic doses fails to raise the free acidity of the stomach during the digestive cycle. The present investigation has confirmed this. Titration of various articles of food, the Rehfuss test meal and fasting juice, to which a known amount of acid was added, against N/10 NaOH, showed that most of the substances tested had definite neutralising power for HC1, and in many instances this was greater than the amount of acid which could be taken in therapeutic doses. By other means also it was shown that the therapeutic administration of HC1 fails to raise the free acidity in the stomach during digestion after a good meal. The suggestion is made to adopt a fixed amount of oatmeal of 2 ounces for the preparation of the test meal.

REFERENCES

- Crohn, B. B.: Am. Med. Sci., 1918, 156, 656.
 Hurst, A. F.: Lancet, 1923, 1, 111.
 Kern, R. A., Rose, E., and Austin, J. H.: Jr. Clin. Invest., 1926, 2, 545.
 Shay, H., Gershon-Cohen, J.: Ann. Intern. Med., 1936, 9, 1628.
 Starling: Physiology, 1941, London.

Gastro-Intestinal Allergy

by

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FOOD allergy, and especially gastro-intestinal allergy, is a rather common condition. Food allergy and gastro-intestinal allergy are not synonymous terms. However, gastro-intestinal allergy is usually due to the intake of certain foods to which the person is allergic. These foods may produce other clinical syndromes at times, e.g. migraine, asthma and eczema without producing gastro-intestinal symptoms. The occurrence of these associated symptoms may be a factor in suggesting the true nature of the intestinal disturbance.

The intestinal symptoms of allergy vary markedly,

and typical syndromes such as are obtained in organic gastro-intestinal lesions rarely occur. Rowe has attributed the following symptoms to gastro-intestinal allergy: aphthae, coated tongue, bad odor of the breath, gastric distension, eructation, epigastric fullness, pyrosis, nausea, vomiting, diarrhea, mucous colitis, constipation, flatulence, pruritus ani, epigastric pain, and pain of the type seen in peptic ulcer. These symptoms could be found in nearly all gastro-intestinal conditions, either organic or non-organic. It can easily be seen from the list quoted above that the establishment of a diagnosis of an allergic affection may be extremely

difficult, and can only be made by meticulous exclusion of all organic ailments. Even in the presence of a history of other definitely allergic manifestations, we have to rule out organic lesions of the gastro-intestinal tract.

Recently, interesting work was done on children with gastro-intestinal allergy by adding to the barium meal a small quantity of the offending food, when X-ray studies were taken. These were compared to other studies made the preceding week with an ordinary barium meal. Nausea was the most frequent reaction. Vomiting occurred in approximately one fourth of the cases. Abdominal pain was found in one fifth of the patients. The pain was cramp-like and was located near the umbilicus, in the epigastrium or in the left upper quadrant. Some of the patients described it as fullness. Two acute abdominal crises simulating a surgical abdomen were also observed. When the allergens were given in the bariumized enema, tenesmus was noted in nearly all of the cases. The authors emphatically point out that there was often a failure of skin tests to correlate positively with the clinical symptoms of gastro-intestinal allergy.

Allergic reactions to food must be carefully considered in every case of abdominal pain. It is not too far fetched to say, that some cases of severe abdominal pain and vomiting may be saved from an operation by an injection of adrenalin. Often the allergic history, physical examination, and the symptoms may be sufficient to supply the lead. Sometimes however, the diagnostic problem is very great. The symptoms of gastro-intestinal allergy, that can be admitted by most sober minded authoritatis, are loss of appetite, nausea, loss of weight, mild epigastric pain, constipation or diarrhea, and acute or chronic colitis. However, it must also be stated that any group of symptoms that cannot be fitted into a definite organic syndrome must be suspected of being allergic in nature. The so called irritable colon may have allergy as its basis; and as can be seen from the discussion of the pathophysiology that follows, ulceration and hemorrhage can also occur. As mentioned above, occasionally an acute surgical abdomen can be simulated.

The pathological changes in gastro-intestinal allergy are definite, but may be transient, if the exposure is short or if vomiting occurs, so that only small quantities of antigen are absorbed. These changes consist of hyperemia, edema and round cell infiltration of the layers of the mucosa of the organs involved. If the antigen is allowed to act only over a short period of time, the condition is reversible and the organ becomes normal. If the process is repeated many times, it can easily be seen that local ischemia, necrosis and sloughing may occur. Finally, induration and fibrosis may be the ultimate result.

Radiographically, hypermotility may be present at an early stage of the syndrome. In the very early stages, before permanent damage occurs, the X-ray findings are usually normal. If the clinical symptoms do not compare with the X-ray findings, gastro-intestinal allergy should at least be given consideration.

The foods most frequently responsible for allergic symptoms are considered to be: wheat, eggs, milk, chocolate, nuts, pork, and sea food, except oysters. Other less liable to give allergic symptoms but still found frequently enough to note are: beans, peas, potatoes, tomatoes, beef and onions. The foods found to give gastro-intestinal symptoms rarely are: lemon, plum, celery, veal, lamb, raspberry and blackberry.

There are two types of gastro-intestinal allergy, the immediate type, which gives immediate reactions and a positive skin test with the offending food; and the delayed type which gives obscure symptoms and a negative skin test. This second type is often very difficult to diagnose. It is found in two varieties, the cumulative type and isolated type. The cumulative type gives symptoms after a long period of time. The isolated type may or may not give symptoms at any particular time, even though the offending food is used.

Before intestinal allergy is considered as an etiological factor in a syndrome, organic lesions of the intestine, parasitic involvements, neurosis, deficiency disease and hyperthyroidism must be considered or effectively ruled out. Allergic reactions are often encountered in the region of the cecum because the fluid chyme reaches this point rapidly and stays there for a time for the absorption of fluid. Thus a marked local reaction can resemble appendicitis, and even actually involve the appendix. The involvement may be transient, but if it goes inexorably onward, operation may have to be resorted to because of the possibility of superimposed organic change. A relationship between gastro-intestinal allergy and peptic ulcer is not generally accepted. While it is believed possible, the condition appears to be infrequent. Since milk is a major allergen, gastro-intestinal allergy should be suspected in ulcer patients that do not do well on a Sippy-type diet.

Biliary colic may infrequently be caused by allergy to various substances. When the patient gives an allergic history, serious thought should be given to the possibility of intestinal allergy. Under the circumstances, the pain may be due to either a reaction in the gall bladder or in the hepatic flexure of the colon.

Either constipation or diarrhoea may be the result of an allergy. Constipation may be due to the spasm of the smooth muscle of the small gut, while diarrhoea may be due to disturbances of peristalsis caused by mucosal swelling. Which is present at a given time, depends on which pharmacological reaction predominates.

Irritable colon is probably the most important colonic condition due to gastro-intestinal allergy. Of course, there may be a superadded neurosis present which will complicate the picture. The patient may have distension, belching, colonic pain, constipation or diarrhoea.

Severe abdominal pain resembling that found in intestinal obstruction may be present in gastro-intestinal allergy. Such cases test the acumen of the most able clinician.

Pruritus ani is sometimes caused by sensitivity to pork, eggs, wheat and occasionally to other allergens. Other more common causes of this distressing ailment, such as dermatophytosis should, of course, be ruled out.

The diagnosis is made by inquiring for an allergic history of the patient's family as well as in the patient. The history may be of any type of allergy. Symptoms occurring every day are usually due to a food taken daily. Symptoms which are seasonal may be due to a food popular during that part of the year. Skin tests and ophthalmic tests are positive in only 50 per cent of the cases. According to Spain valuable clues can be obtained by asking the patient the following three questions:

1. What foods are taken to excess?
2. What foods are eaten, though disliked?
3. What foods are eaten though they caused symptoms during youth?

Another help in diagnosis is a so-called food diary. In this the patient lists all the food he has eaten that day, and notes any symptoms that were present during the same day. This diary must be kept for at least a month in order to discover foods that may give a delayed reaction. Another very important method of determining allergic foods is by an elimination diet. In this diet (Figure I) foods are given which are known by experience to offend very few people, and then other foods are added one by one until symptoms are experienced, or until a fairly liberal diet is given to the patient. Amongst the carbohydrates, rice is a food that rarely causes symptoms. Later corn, tapioca and potatoes may be substituted or added. Lamb is the best form of protein with which to start the diet. Gelatin, chicken, bacon, soy beans and lima beans may be added later. Of the fats, cotton seed oil and later olive oil, corn oil and finally butter that has been thoroughly washed free of milk, are best. Of the vegetables, lettuce, carrots, spinach, artichokes, beets and asparagus are added in this order. Among the fruits, pear, lemon, grapefruit and pineapple are known to give the least symptoms. Since this diet is extremely limited in both vitamins and minerals, they must under all circumstances be included. If no milk is taken, it is extremely important to add a sufficient amount of calcium.

Treatment of gastro-intestinal allergy consists in eliminating the offending foods completely. Attention should be paid to foods in which small quantities of the

allergens are found. Desensitization by giving extremely small quantities of the allergenic food and increasing the quantity each day has not been sufficiently successful, although praised by some authorities. Ingestion of small amounts of the allergens before each meal has likewise produced mediocre results.

Vitamin C detoxification has recently been advised. Vitamin C in large doses, (500 mg. per day) may detoxify a minor allergen (one occasionally causing symptoms), but it would be unfair to expect it to detoxify a food to which the subject is overwhelmingly allergic. In my hands, eliminating the major allergic substances, and prescribing the indicated doses of Vitamin C, seems to have given the best results.

Figure I

Elimination Diet

Use the diet listed directly below for two days.

If no symptoms, substitute or add one of the following foods every 2 days. Keep any diet selected at least 2 days. Add one new food in one category at one time.

BREAKFAST

Juice: Lemon Juice	Juice: Grapefruit juice, pine- apple, pear
Cereal: Boiled rice (boiled in water)	Cereal: Rice flakes, corn flakes
Baked Goods: Rice muffin	Baked Goods: Corn bread, rye bread, rye muffin
Spread: Grapefruit marmalade	Spread: Lemon jelly, pear butter, pineapple jam

LUNCH

Salad: Lettuce	Salad: Carrots, spinach and beets
Cotton seed oil may- onnaise	Corn oil mayonnaise
Pear	Grapefruit, lemon, peach, pineapple
Meat or other protein: Lamb or lamb chops	Meat or other protein: Roasted chicken, oysters, soy beans, peas, veal and bacon
Soup: Lamb broth with rice	Vegetables: Carrots, beets, squash and potatoes
Vegetables: Cooked spinach	Spread: Carefully washed butter
Baked Goods: Rice muffin	Desserts: Tapioca or corn starch pudding or gelatin pudding.
Spread: Cotton seed oil	
Desserts: Rice pudding	
Beverage: Tea	

SUPPER

Repeat lunch meal.

SUGGESTED READING

1. Alvarez, W. C., Hinshaw, H. C.; Foods that Commonly Disagree with People. *J.A.M.A.*, 104:2053, June 8, 1935.
2. Rowe, A. H.; Clinical Allergy Due to Foods, Inhalants, Contactants, Fungi, Bacteria and Other Causes. 1931, Philadelphia, Lea and Febiger, P. 111.
3. Spain, W. C. In Bridges, M. A., Dietetics for the Clinician. 1941, Philadelphia, Lea and Febiger, P. 242.
4. Andresen, A. F. R.; Gastro-Intestinal Allergy, Its Present Status. *Southern Med. J.*, 34:418, 1941.
5. Fries, J. H., Zimor, J.; Gastro-Intestinal Allergy in Children. *J. Pediatrics*, 16:69, 1940.
6. Concord, R. J.; Gastro-Intestinal Allergy. *Brasil-Medico*, 54:455, July 1940.
7. Holmes, H. N.; Food Allergy and Vitamin C. *Annals of Allergy* 1:235, 1943.

Vitamin E vs. Wheat Germ Oil

By

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THE literature reporting the advantages to be gained by the use of wheat germ oil, or vitamin E, in the treatment of various types of muscular disturbances is so confusing in respect to the type of material used, that this note is submitted with the hope that it will aid in clarifying the situation.

This statement seems especially important in view of a recent report by Vogt-Moeller (1). In a symposium held in London in 1939 Vogt-Moeller stated "Finally, let it be kept in mind that wheat germ oil, which so far has been the preparation most commonly employed for therapeutic trials, may contain many biologically active substances other than Vitamin E, and one must consider the possibility that some of these may have contributed to the observed effects. Even though this appears to me rather unlikely, the question can soon be settled with certainty by repeating the experiments with pure tocopherols."

In the recent work referred to above, Vogt-Moeller gives the results of just such an experiment. He points out that the various reports on the influence of vitamin E on neuromuscular disorders are confusing because vitamin E was used in some experiments while wheat germ oil was used in others. It has been shown previously that wheat germ oil contains factors other than vitamin E (2). Certain investigators (3) postulated that several factors may be involved in the positive results obtained in treating neuromuscular disturbances, and that vitamin E was not alone in bringing about beneficial results.

Because Vogt-Moeller's paper is not readily accessible in this country, a fairly detailed report of it is included in this communication.

Dogs attacked by the distemper virus usually develop typical neuromuscular symptoms. Vogt-Moeller planned an experiment involving 90 dogs affected by this disorder. All dogs, including the controls, were placed on a balanced diet with a supplementary vitamin B complex preparation. Before instituting treatment, he waited until all dogs had developed the initial symptoms of distemper. These usually preceded the development of neuromuscular disturbances.

Thirty dogs were the control group.

Thirty dogs were injected daily with 10 milligrams of tocopherol (vitamin E).

Thirty dogs were injected daily with 5 c.c. of wheat germ oil, which contained approximately 10 milligrams of alpha tocopherol.

It appears that, for the first time, evidence has been presented of the presence in wheat germ oil of a factor that exerts a beneficial effect in neuromuscular disturbances other than vitamin E. For many years we, in our laboratory, have suggested that research workers

in reporting their work make a sharp distinction between vitamin E (tocopherol) and wheat germ oil. Vogt-Moeller's work now makes such differentiation imperative.

The results are tabulated as follows:

Treatment	Control	Tocopherol	Wheat Germ Oil
Total number of dogs	30	30	30
Died	14	16	12
Dogs developing neuro-muscular symptoms—died	10	11	3
Dogs developing neuro-muscular symptoms—survived	11	12	2
Total developing neuro-muscular symptoms	21	23	5

The effect of Vogt-Moeller's work will be far reaching for it will demand a reexamination, reappraisal and, in many instances, a repetition of much of the work already done in this field. Research has long been subjected to such penalties but, while it makes progress slow, it assures an ever closer approximation of the truth.

The various reports in which the statement is made that vitamin E does not control habitual abortion can no longer be given full credence. The work of Currie (4) and others (5, 6, 7) must, somehow, be fitted into the picture. Furthermore, it would seem that doubt should be given to the statements that vitamin E will not help cows and sows to conceive rather than to the reports of Vogt-Moeller (8) and others (9, 10, 11, 12, 13) that wheat germ oil is successful in treating 'shy breeding.'

Among those reports where the statement is made that it was not possible to confirm a given work even when using wheat germ oil, it would be desirable to know something about the nature of the oil used. Was the oil "cold pressed" or solvent extracted? What were the temperatures involved? What was the nature of the solvent used? What was the age of the oil? To a great degree, the answers to these questions hinge mainly on two points, namely; the stability of the oil and the presence of substances in the oil other than the tocopherols. The incorporation of tocopherols other than the alpha form in vitamin E concentrates might be considered an admission of the fact that the performance of vitamin E (alpha tocopherol) was disappointing.

Mackenzie, Mackenzie and McCollum (14) indicate the importance of stability. In their work, the pressed oil was unfit for making their concentrate of vitamin E; only the solvent extracted oil could be used. Shute (15) states that the wheat germ oil he used (pressed) will lose its value for treating habitual abortion in 8

days unless it is kept in the cold. Pressed wheat germ oil is obviously not the same product as solvent extracted wheat germ oil. It is important to note that Currie's work was done with a concentrate of a solvent extracted oil (Glaxo). A similar product was used by Hain and Sym (16) in their work on the control of menopause flushes. Other investigators have called attention to the difference in character of extracted and pressed oils (17). Yet, it should not be assumed that a pressed wheat germ oil will not be effective. These considerations emphasize the point made above, that the wheat germ oil should be stable, whether it is pressed or solvent extracted. Should the factor postulated by Vogt-Moeller be unstable, there is a likelihood that this factor is not present in wheat germ oil that has a high free fatty acid content or a high peroxide value.

It is commonly understood that vitamin E is unstable. On the contrary, vitamin E in foods is quite stable. It is far more stable than vitamin A. In our own laboratory, rancid pressed wheat germ oil with a 30 m.e. peroxide value and 18 per cent f.f.a. (free fatty acid) revealed three-fourths of the quantity of vitamin E present in pressed oil containing 2 per cent f.f.a. and a 3 m.e. peroxide value. Ordinary livestock feed subjected to room temperature for one year retains adequate vitamin E as we understand livestock requirement. This stability of vitamin E and its widespread

occurrence in foods should be considered in the light of Shute's views on the instability of the factor that controls habitual abortion. May it be that this factor is not vitamin E at all?

It appears that studies involving vitamin E should specifically state the manner in which the vitamin was prepared, its form and its source as well as the stability of the material used. Tests should be made for its stability throughout the course of the experiment.

Finally, the fact that a stable wheat germ oil appears to be effective in preventing neuromuscular disorders in dogs affected by distemper, while vitamin E alone seems ineffective, should stimulate studies to elucidate further Vogt-Moeller's suggestion that solvent extracted and stable wheat germ oil contains factors other than the tocopherols which exert a beneficial effect in such disturbances.

It must be concluded that dismissal of wheat germ oil as an effective aid to breeding of livestock, and as an aid to contributing to viability of the young, by those who have assumed that it is ineffective because there is plenty of vitamin E in most rations, or by those who have had negative results with a wheat germ oil of variable and questionable origin and undetermined stability, is unwarranted.

Only controlled experiments with a wheat germ oil of known stability and of constant and satisfactory origin can clarify this important problem.

REFERENCES

1. Vogt-Moeller, P.: Tierartzl. Rundschau, 48:274 (1942).
2. Martin, G. J.: J. Nutrition, 13:679 (1937).
3. Goettsch, M., and Ritzmann, J.: J. Nutrition, 17:371 (1939).
4. Currie, D. W.: Brit. Med. J., II, 1218 (1937).
5. Vogt-Moeller, P.: Klin. Wschr., 15, 1883 (1936).
6. MacDonald, C. R.: Report of Conference on Vitamin E. British Medical Society 1, 943 (1939).
7. Cromer, J. K.: Med. Ann. Dist. Columbia, 7, 145 (1938).
8. Vogt-Moeller, P., and Bay, F.: The Veterinary J., 87, 165 (1931).
9. Tutt, J. P.: The Veterinary J., 89, 416 (1933).
10. Vogt-Moeller, P.: Vitamin E, A Symposium, Chem. Publ. Co., Page 57 (1939).
11. Lehmkopf, H.: Berl. U. Muneh. Tierartzl. Wschr., 367 (1936).
12. Strassl: Berl. U. Muneh. Tierartzl. Wschr., 397 (1938).
13. Schioppa, L.: Zeit. F. Vitinforsch., 8, 132 (1938).
14. Mackenzie, C. G., Mackenzie, Julia B., and McCollum, E. V.: Public Health Reports, 53, 1779 (1938).
15. Shute, E.: Amer. J. Obst. and Gynee., 35, 609 (1938).
16. Hain, A. M., and Sym., J. C. B.: British Medical J., 8, July 3, 1943.
17. Parker, W. E., Neish, A. C., and McFarlane, W. D.: Can. J. Res., 19, 20 (1941).

Failure of Intestinal Bacteriostasis Following Administration of Pectin to the Rat

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A NUMBER of reports have appeared concerning the bactericidal properties of pectin preparations (1-6). In general these indicate that pectin *per se* exerts no bactericidal effect, although the pH of some pectin preparations and the acidic by-products of pectin digestion by intestinal microorganisms were responsible in some cases for a decrease in the number of test organisms observed in *in vitro* studies. When experimen-

tal solutions were buffered to correspond with conditions present in the intestinal tract, no bactericidal action attributable to pectin was observed. In contrast to these studies nickel pectinate has been shown to possess bactericidal properties both clinically in man (7) and in *in vitro* experiments with intestinal microorganisms (1,3,4,5).

It has been demonstrated by a number of investigators that although rats will grow and reproduce on purified rations containing six B complex factors

(thiamine hydrochloride, riboflavin, pyridoxine hydrochloride, calcium pantothenate, nicotinic acid and choline chloride), incorporation of sulfaguanidine or sulfasuxidine in such rations results in retardation of growth, alopecia, spectacled eyes, ophthalmitis, porphyrin-caked whiskers, achromotrichia and other manifestations of dietary inadequacy presumably due to inhibited synthesis of essential factors by intestinal microorganisms (8-11). The development of these symptoms in animals maintained on a similar ration but containing a suspected bacteriocide might accordingly be used as a physiological indicator of intestinal bacteriostasis. In the following experiment pectin and nickel pectinate were incorporated in a purified ration containing the B complex factors listed above and

Table 1
Composition of Experimental Diets and Distribution of Rats.

	A	B	C	D	E	F	G	H
Pectin ¹		2.5	5	10				
Nickel pectinate ²					2.5	5	10	
Sulfaguanidine								1
Sucrose	73.5	71.0	68.5	63.5	71.0	68.5	63.5	72.5
Vitamin Test								
Casein ³	22.0	22.0	22.0	22.0	22.0	22.0	22.0	22.0
Salt Mixture ⁴	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Number of animals in group	6	4	6	6	4	6	6	6

To each kg. of the above mixture were added the following synthetic vitamins: thiamine hydrochloride 20 mg., riboflavin 20 mg., pyridoxine hydrochloride 20 mg., calcium pantothenate 100 mg., nicotinic acid 100 mg., choline chloride 1200 mg. and 5 mg. 2-methyl-naphthaquinone. In addition each rat received the following daily supplement: corn oil (Mazola) 800 mg., alpha-tocopherol 0.5 mg., and a Vitamin A-D concentrate containing 50 U.S.P. units of vitamin A and 5 U.S.P. units of vitamin D.

1. N.F. Pectin, California Fruit Growers' Exchange, Ontario, California.
2. Pectalin Powder, containing 0.5 per cent nickel as nickel sulphate, Emory W. Thurston Laboratories, Los Angeles, California.
3. S.M.A. Corporation, Chagrin Falls, Ohio.
4. Salt Mixture No. 1 (Sure (12)).
5. Nopec Fish Oil Concentrate, assaying 800,000 U.S.P. units of vitamin A and 80,000 U.S.P. units of vitamin D per gram.

REFERENCES

1. Arnold, Lloyd: The bactericidal action of pectin and metal pectinates. *Amer. J. Dig. Dis.*, 6:104, 1939.
2. Prickett, P. S. and N. J. Miller: Effect of pectin on bacterial growth. *Proc. Soc. Exp. Biol. and Med.*, 40:27, 1939.
3. Prickett, P. S. and N. J. Miller: In vitro effect of pectin and nickel pectin on bacterial growth. *J. Ped.*, 15:710, 1939.
4. Haynes, E. C., A. Tompkins, G. W. Crook and M. Winters: Bactericidal action of pectin containing nickel. *Proc. Soc. Exp. Biol. and Med.*, 37:478, 1938.
5. Myers, P. B. and A. H. Rouse: Pectinates, with special reference to nickel pectinate and their therapeutic value. *Amer. J. Dig. Dis.*, 7:39, 1940.
6. Werck, S. C., R. W. Jung, H. Plenk, A. A. Day and A. C. Ivey: Pectin and galacturonic acid and intestinal pathogenesis. *Amer. J. Dis. Children*, 63:839, 1942.
7. Elvehjem, C. A., Tarek Ismail and B. H. Green: Pectin and nickel pectinate in acute and chronic bacillary dysentery. *Amer. J. Dig. Dis.*, 6:56, 1939.
8. Black, S., J. M. McRae and C. A. Elvehjem: Use of sulfaguanidine in nutrition experiments. *Proc. Soc. Exp. Biol. and Med.*, 47:308, 1941.
9. Black, S., R. S. Overman, C. A. Elvehjem and K. P. Link: The effect of sulfaguanidine on rat growth and plasma prothrombin. *J. Biol. Chem.*, 145:137, 1942.
10. Welch, A. D.: Succinyl-sulfathiazole as an inhibitor of bacterial synthesis in nutrition experiments. *Federation Proc.*, 1:171, 1942.
11. Welch, A. D. and L. D. Wright: The role of "folic acid" and biotin in the nutrition of the rat. *J. Nutrition*, 25: 555, 1943.
12. Sure, B.: Dietary requirements for fertility and lactation XXIX. The existence of a new dietary factor essential for lactation. *J. Nutrition*, 22:449, 1941.

* From the animal colony, Department of Biochemistry, University of Southern California. Kindly provided by Dr. H. J. Deuel, Jr.

** Purina Dog Chow supplemented once weekly with lactose.

*** Food and water consumption were voluntarily reduced subsequent to the first day of feeding. Animals resembling in gross appearance and length of survival a subsequent group were fed at a similar age and weight but survived to death. The possibility of nickel toxicity at this level has not been excluded.

The Advantages and Disadvantages of the Old and Newer Insulins

Presented by Dr. L. Bauman at New York Post-Graduate Medical School and Hospital April 4, 1944 at 4 P.M.

BEFORE proceeding to the assigned topic it might be well to review certain considerations that have a bearing on my conception of the disease.

1. At the outset a diabetic is a normal person with an insulin deficiency. Therefore a normal diet suited to the individual's nutritive state, activity and age is prescribed without regard to the underlying disease. A low calorie maintenance or high calorie diet is given according to whether the patient is overweight, normal or underweight. If the amount of insulin exactly neutralizes the deficiency, a return to the normal state should ensue. By the same token such an individual should not develop the dreaded complications of the disease, namely, diabetic retinitis, cataract and early arteriosclerosis.
2. By complete regulation we understand the constant maintenance of normal blood sugar levels. We realize that this ideal may not be easily achieved, but every effort should be made toward this direction. Practically there are a number of obvious difficulties. The main difficulty is our ignorance of the mechanism of insulin action. No decrease in glucose content is observed when insulin is added to blood *in vitro*.
3. What are the complimentary ferment, coferments or other substances that participate in insulin activity and enable storage of glucose (as glycogen) or its degradation to carbon dioxide and water. We know that phosphoric acid esterification is necessary and that pyruvic acid is an intermediate in glucose oxidation, but thus far the role that insulin plays in this chemical activity is not clear. The remarkable work of the Coris at St. Louis awakens hope that this problem may be solved in the not too distant future, and then a more intelligent therapy should develop.
4. Another practical difficulty is the influence of emotions on the diabetic state. At times this influence is not readily discernible, but clinical experience warrants the belief that in some, the unfavorable effect of emotional tension and lability makes consistent regulation impossible. In such patients a compromise is all that can be achieved. Recent work has shown that sympathetic and parasympathetic impulses lead to the discharge of substances that are powerfully active, physiologically and these may play a role in causing this difficulty.

Even diabetic children are subject to this emotional influence. At the Pediatric Clinic of Iowa State University meticulous regulation is the rule. Each child remains at the University Hospital for a minimum period of six weeks. During this time stabilization ensues and persistent sugar freedom is the rule. According to Dr. Jackson, if such a child is told that his mother will visit him, he is apt to pass sugar soon afterward.

Submitted April 11, 1944.

At the present time we have

1. Uncombined
2. Globin
3. Protamine

insulins at our disposal. I have had no experience with the mixtures of uncombined and protamine zinc insulin. As the action of plain insulin is shortlived, its use in uncomplicated diabetes is rather limited. It is used when one has to proceed carefully on account of the danger of insulin shock as in old people or people with coronary disease. In such cases death from coronary thrombosis or cerebral thrombosis secondary to insulin shock is not too infrequent.

In gastric upsets due to one cause or another and where the regular consumption of meals is uncertain, several doses of plain insulin seem safer.

Immediately preceding and following operations the use of several doses of plain insulin during the day seem more logical and safer than one larger dose of depot insulin in the morning.

In diabetic coma where rapid action is imperative, repeated doses of regular insulin are preferable.

Personally, I use plain insulin chiefly as an adjuvant in severe cases where a large dose of protamine zinc or globin zinc insulin is required.

A dose of protamine zinc insulin large enough for a twenty-four hour control may induce hypoglycemia after midnight, whereas a comparable dose of globin zinc insulin may unduly depress the blood sugar between four and five P.M. In either case, the amount is decreased by 10 or 15 units, and this is replaced with standard insulin. The two injections are given one hour before breakfast in separate syringes. Usually it is possible by shifting the carbohydrate distribution to maintain control with a single dose of depot insulin.

At the present time I am impressed by the advantage of globin zinc insulin over protamine zinc insulin. It is a clear solution with little antigenic activity effective during the three meal period with maximum hypoglycemia in the afternoon when insulin shock is more apt to be detected than during the night.

If 1/5 of the carbohydrate allotment is given at breakfast, 2/5 at lunch and 2/5 at dinner, efficient control is usually obtainable with a single dose of globin zinc insulin.

However, experience in all fields of medicine elicit individual differences, and so in diabetes modifications have to be made to suit the particular patient.

I refer to further change in distribution of carbohydrates, additional snacks in the afternoon or before retiring.

In some cases that Dr. Mosenthal has carefully studied, the addition of a small dose of protamine zinc insulin with a corresponding decrease in globin zinc insulin given separately before breakfast may dovetail

in a most gratifying manner and produce effective control when every other combination has failed. I have had a similar experience at the Presbyterian Hospital in a limited number of cases. However, during the past seven years globin-zinc insulin has controlled a number of severe diabetics that did not respond satisfactorily to protamine zinc insulin.

The inexperienced physician is apt to err in several respects:

- 1st—In the idea that all diabetics are easy to regulate.
- 2nd—In not allowing ample time for the body to adjust itself to a diet and insulin dosage before making a change.
- 3rd—In encouraging careless habits of control.

Editorial

ALLOXAN DIABETES

TH E N. Y. Diabetes Association is comparatively young; however its activities are of great importance. It has been the policy of this Journal to publish the transactions of this society whenever possible. We are sorry that we are not able to publish in full the meeting of September 28th due to other special arrangements. This is regrettable, the more so as the N. Y. Diabetes Association gave the opportunity to two young scientists to discuss one of the most important problems in the field of diabetes.

Dr. Martin H. Goldner from the University of Chicago discussed "Alloxan Diabetes". He reviewed some of the findings which have impressed all of those interested in this field. For, we are now dealing for the first time with a real diabetes caused by some chemical, Alloxan. Alloxan is the derivative of uric acid and is known to science for about one hundred years. Dunn, Sheehan, and McLetchie^{1,2} were the first to record that one injection of Alloxan caused two distinct phases, first, a sudden rise in the blood sugar level for several hours, second, a severe hypoglycemia. It was the work of the speaker and his collaborators to find a third phase, a continuous hyperglycemia following the hypoglycemia. This proved to be one of the signs of a real diabetes, for it was definitely influenced and could be controlled by protamine zinc insulin. Besides, the animals showed all signs of a real diabetes. Goldner was able to report that some animals were alive more than one year after the one injection of Alloxan and continued to be diabetic.⁴

To produce diabetes in animals is not always very easy. There are some animals which do not show any symptoms of diabetes, even after total extirpation of the pancreas. Goldner was able to induce this metabolic condition with one injection of Alloxan and keep the animals alive. It was only important to watch the animals carefully the first day after the injection, for otherwise the animals would die during the above mentioned second hypoglycemic phase. The blood sugar sank so low that glucose had to be given intravenously to combat shock.

During the third phase, the hyperglycemic one, the blood sugar level was three times to six times as high as before administration of Alloxan. Goldner showed some of the curves after sugar tolerance tests. The animals reacted to protamine insulin just like a case of real diabetes. This "chemical" diabetes might permit us to study diabetes from many new angles, as the

speaker revealed that his experiments had been performed on many different types of animals (dogs, cats, pigeons, and rabbits).

He was reluctant to discuss the implications to human patients, not going further than previously mentioned.³ He had given Alloxan to a case of an insulin producing islet cell carcinoma of the pancreas without any influence on the sugar or non protein nitrogen levels of the blood.

Goldner and Gomori then discussed the pathological findings in diabetes and in Alloxan diabetes. Up to now it is very difficult to find pathological anatomical changes in the pancreas in diabetes. Only if the specimens are stained by a special method, which Gomori perfected, are we able to see changes. He differentiates between alpha and beta cells, the one showing up in reddish color, the other appearing to be blue in this particular stain. He showed the gradual elimination of the beta cells after the injection of Alloxan. This takes place within a few hours. In some experiments, the authors clamped the blood supply of that part of the pancreas for five minutes. The pathological examinations of these specimens revealed that those parts which had been reached by the Alloxan failed to show stained beta cells, whereas those clamped off parts of the pancreas, showed the normal number and well-stained cells. In the discussion, Bailey from Boston contributed his findings that he was able to find Alloxan for only five minutes in the blood with his special method. After that time, the substance had disappeared, showing a very rapid absorption by the tissue.

When large amounts of Alloxan were given, other organs like kidneys and liver, showed necrosis, however, in case of administration of tolerable amounts, it seemed as if the substance was selectively acting only on the islet cells. Up to now we know of no other substance which acts so selectively on a certain type of highly differentiated cells.

Probably the most important findings were the following: (1) An inflammatory reaction could not be found in any case, which is very surprising. (2) In pigeons the authors found far advanced visceral gout with very high uric acid levels in the blood. This brings us to the question of how far the often noticed appearance of these two metabolic diseases, diabetes and gout, is due to the same underlying disturbance. Goldner and Gomori have indicated a new road in experimental medicine.

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REFERENCES

1. Dunn, Shaw J., Sheehan, H. L., McLetchie, N. G. B. Neerosis of Islets of Langerhans Produced Experimentally. *Lancet*: 1,484. April 17, 1943.
2. Experimental Selective Neerosis of the Island of Langerhans. *J.A.M.A.* 122, 10,676. July 3, 1943.
3. Brunschwig, Allen, Goldner, Gomori. Alloxan. *J.A.M.A.* 122, 14,966. July 31, 1943.
4. Experimental Diabetes. *J.A.M.A.* 124, 1,38. Jan. 1, 1944.

Book Reviews

X-Ray Examination of the Stomach. By Frederic E. Templeton. Pp. 516, (\$10.00), Chicago, University of Chicago Press, 1944.

Dr. Templeton has produced one of the best treatises on the x-ray examination of the stomach written in the English language. The text shows meticulous care in planning the author's approach to the subject, and it is refreshing to see well arranged and well printed illustrations all in the negative as the films appear when shown by transmitted light. Every phase of the examination of the esophagus, stomach, and duodenum is covered. Pathology is well illustrated. The discussions of the pathological physiology in the various projections of the stomach are particularly good. The description of the normal and pathological physiology of the esophagus are excellent. This book will, in our opinion, become a standard reference for both the practitioner and radiologist.

The University of Chicago Press has done an excellent piece of work in the printing of both the text and illustrations. One of the difficulties of most roentgen atlases and roentgen articles has been to see what the author wished the pictures to convey, but this difficulty certainly is not the case in Dr. Templeton's monograph. This book is a timely "must" addition to the medical literature.

The Diet Therapy of Disease. By Louis Pelner. Pp. 143, New York, Personal Diet Service, 1944.

One of the main reasons the study of dietetics in the treatment of disease has not received the attention it deserves has been the time required to assemble and correlate the data. Any work which will reduce this to a minimum and without too much "digging" is certain to fulfill a long-felt need for most practitioners. In Dr. Pelner's book, this need has been definitely met by presenting a long list of representative diets in brief, accessible form. The material in the book is well arranged, the diets being listed in alphabetical order. Preceding the diet is a presentation of the salient features of the disease and the rationale for its use. As a background, the most common foods and their caloric and vitamin values are presented, accompanied by illustrations and charts. There is also a resume of the role played by the various food components in the metabolism of the body. The number of diets is quite comprehensive, ranging from "Acid Ash Diet" to a very complete group on "Ulcer." This latter group includes the Andresen and Meulengracht diets for bleeding ulcer, as well as those for the acute

and ambulatory patients. Under gallbladder disease, he points out that a high fat diet is beneficial in the early case of cholecystitis, before stones have formed. Also the idea that proteins are injurious in liver disease has been shown to be incorrect. Other interesting points are the classification of hypoglycemia under the diet for hyperinsulinism, and a presentation of the causes of arthritis. Dr. Pelner does not forget to warn the reader that many of these diets are deficient in vitamins which must be supplied in sufficient amounts. This is an excellent book, and will prove to be a distinct help to all those who have occasion to use diet therapy.

Roentgenographic Technique. By D. A. Rhinehart, Pp. 471, (\$5.50), Philadelphia, Lea & Febiger, 1944.

Dr. Rhinehart, in this third edition of his book on Roentgenographic Technique, has produced a valuable manual for the profession, the student, and the technician. The first half of the book is given over to just the right amount of physics for the beginner and the technician; and the discussions of the dark room technique and methods of experimentation for the student are particularly worthwhile.

Thereafter the author explains by illustration and text the technical procedures in a very adequate manner and gives an excellent bibliography with each chapter dealing with the particular part discussed. Except for a few minor errors, the volume is well compiled in its entirety. It has 201 good illustrations, and can be recommended for the radiologist and particularly the student technician.

Trichinosis. By Sylvester E. Gould, M. D., Pp. 322, 122 illustrations, (\$5.00), Springfield, Illinois, Charles C. Thomas, 1944.

This unique book deals with trichinosis from every conceivable standpoint and, for the first time, places between two covers, all that is known about a serious and sometimes fatal infestation. The author has shown great judgment in his method of attack, so that every chapter, whether dealing with symptoms, treatment, public health aspects, diagnosis, or the historical phases, is exhaustive yet plainly written and helpful. 128 case histories are included. Undoubtedly this book should enjoy a wide sale because most physicians are conscious of knowing far too little about this disease, its diagnostic difficulties and its potential seriousness.

A Surgeon's World. By Max Thorek. Pp. 410, (\$3.75). Philadelphia and New York, J. B. Lippincott Co., 1943.

This is the autobiography of a distinguished surgeon, author, and editor of medical texts. Dr. Thorek has met many of the great and near great of this century, in both the medical profession and other fields, and tells many an amusing tale about them. Particularly interesting will be found his account of researches on the questions of sex and rejuvenation. He describes

his contacts with such men as Voranoff and Steinach, men whose labors were distorted and popularized by the press as rejuvenation by "monkey glands."

The book is written with a great sense of humor and kindness, as indeed one would expect in a man whose life has been somewhat along the style of an Horatio Alger hero. The book makes interesting reading and should prove an entertaining gift for the medical student or the layman who is interested in lives of the men who look after his welfare.

Abstracts of Current Literature

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CLINICAL MEDICINE

MOUTH AND OESOPHAGUS

TORESON, W. E.: Secondary carcinoma of the esophagus as a cause of dysphagia. (*Arch. Path.*, v. 38, p. 82, Aug., 1944.)

A statistical study of 599 autopsies of metastasizing carcinoma showed secondary involvement of the esophagus in 3.27 per cent. Of 26 metastasizing tumors studied, 24 were carcinoma, one was lymphosarcoma, and one melanoma. Original tumors were of the stomach, breast, larynx, pancreas, testis, eye, tongue, bronchus, mediastinal lymph nodes, prostate and tibia. Metastasis alone accounted for 30 per cent of the spread.—W. J. Snape.

JONES, H. EVERLEY, T. G., ARMSTRONG, H. F., GREEN, AND V. CHADWICK: Stomatitis due to riboflavin deficiency. (*Lancet*, v. 246, p. 720, 1944.)

Stomatitis was observed in 1746 of 10,313 men in a camp in North Africa. On a diet containing an average of 1.61 mg. of riboflavin daily the camp population had been free from stomatitis, but this condition developed 2 months after the daily intake was reduced to about 1 mg., and was not abolished by an intake of 1.28 mg. in the following month. It yielded rapidly to treatment either with 100 mg. of riboflavin in 5 days or with $\frac{1}{2}$ ounce of fresh yeast daily. The lesions on the tongue were studied with a slit-lamp and flattening of surface papillae, loss of ramification of down-growing epithelial processes and complete cessation of epithelial growth were observed.—Courtesy Biological Abstracts.

STOMACH

BROWN, D. C., AND McHARDY, G.: Postgastrectomy gastritis. (*Annals Internal Med.*, v. 20, p. 789, May, 1944.)

Post-operative gastritis, as a result of sub-total gastrectomy, has not received the attention it deserves. Although it is a very frequent complication, there is no syndrome characteristic of this lesion. It is due to a combination of the superficial and hypertrophic varieties, and may involve the entire remnant, but it is usually more severe in the anastomotic area. It frequently extends into the jejunum. A rhythmical stoma is usually present. The gastric rugae are quite edematous and have a turgescence red color, often pitted with minute erosions. They may be covered with a yellowish-grey mucus, while the separating furrows are filled with a purulent material. Achlorhydria is the rule. Severe causative factors are given as tending to produce the condition: a chronically ill patient, severe trauma, achlorhydria and bacterial flora, a poorly functioning stoma, the use of hydrochloric acid for relief postoperatively, improper dietary regulation. The prognosis is fair. Dietotherapy, vitamins, liver extract parenterally are among the therapeutic measures suggested for its correction. Relief by alkali is frequently obtained.—H. M. Metzger.

MILLER, J. R., AND EUSTERMAN, G. B.: Mikulicz' syndrome: report of a case with associated pulmonary and gastric lesions. (*Proceed. Staff. Meet. Mayo Clinic*, v. 19, p. 425, Aug. 23, 1944.)

Mikulicz' syndrome is a symptom complex characterized by symmetrical swelling of the lacrimal, orbital and salivary glands. It is the result of infiltration of the areas involved by small round cells. The findings may be due to a systemic disease such as lymphoblastoma or leukemia, or to a distinct disease entity, Mikulicz' disease. The case history of a 74 year old man is presented who in addition to lacrimal and salivary findings showed unusual associated findings in the stomach and lungs. These responded well to

roentgen therapy. In discussing this paper, Dr. E. T. Leddy brings out several important points—1) For the purpose of roentgen treatment Mikulicz' disease should be regarded as a manifestation of lymphoblastoma rather than a specific disease. 2) Gastroscopy or laparotomy should be performed in any gastric condition where diagnosis is not certain. 3) A therapeutic test by roentgen ray should be done. If the lesions improve in three weeks, then the lesions probably were lymphoblastoma; if no improvement is shown then the lesions may be carcinoma.—J. M. Theone.

KIRBY, A. H. M.: *Attempts to induce stomach tumors. III. The effects of (a) a residue of cholesterol heated to 300°C., and (b) ▲ 3, 5-cholestadiene.* (*Cancer Res.*, v. 4, p. 94, 1944).

Rats on an adequate basal diet fed the residue left from cholesterol heated to 300°C after the removal of dicholesteryl ether and ▲ 4-cholestenone, at a level of 20 mg. daily for 2 years, showed no tumor of the fore-stomach nor of the glandular zone. Other rats fed ▲ 3, 5-cholestadiene at a level of 25 mg. daily for 2 years plus an adequate basal diet, showed no tumor in either part of the stomach. It seems unlikely that this diene is concerned in the avitaminosis A induced by feeding heated fats to rats. A large, inorganic bladder stone is reported in 1 rat of this series.—Courtesy Biological Abstracts.

BOWEL

LEE, M. J., JR.: *Congenital anomalies of the lower part of the rectum.* (*Am. J. Dis. Child.*, v. 68, p. 182, Sept., 1944.)

The normal embryology of the anal and rectal regions is described. It is believed that many malformations of these regions develop from abnormalities in the development of the embryo during the seventh or eighth weeks. It is during this period that a primary perineum is established and the urogenital sinus acquires an external opening.

Four types of malformations are listed: 1. Incomplete rupture of the anal membrane 1 to 4 cm. above the anus. 2. Persistent anal membrane causing imperforate anus. 3. Imperforate anus and a rectal pouch that is a closed sac. 4. Anus and anal pouch normal but a blind rectal pouch.

Symptoms, roentgen findings, associated anomalies and treatment are discussed and 16 case histories are presented. The author points out that fistulas between the rectal and genitourinary tracts are quite frequent.—R. L. Burdick.

GRIMSON, K. S., VANDERGRIFT, H. N. AND DRATZ, H. M.: *Management and prognosis of megacolon (Hirschsprung's disease).* (*Am. J. Dis. Child.*, v. 68, p. 102, Aug., 1944.)

Cases of megacolon seen at the Duke Clinic are reviewed. Of 24 patients, 21 were treated by usual types of medical management, consisting of diets, autonomic drugs, enemas and laxatives. Fecal impaction in one case and volvulus of the sigmoid in two cases required emergency operations. Remission of symptoms occurred in six of the 21 patients without recourse to surgery. Sympathectomy resulted in remission of symptoms in one case. Five of the 21 cases are now dead. At an early period three of the 24 cases had one stage resection of the megacolon and ileo-sigmoidostomy and are now living and well. The authors believe that megacolon may be divided into three categories, each characterized by the extent to which the colon is involved: 1. Uniform dilatation of the whole colon, including a dilated or easily dilatable rectum. 2. Dilatation of the proximal segment of colon, with a seminating normal segment and a normal colon. 3. Extensive enlargement of the sigmoid colon or sigmoid and descending colon, either with a dilated proximal colon or normal proximal colon and rectum. The first group can be treated by conventional medical management providing the diet is maintained adequate. The second group should be subjected to surgery. Protracted medical management for the third group is believed to be justified.—G. Klenner.

LEHMAN, E.: *Psychogenic incontinence of feces (encopresis) in children.* (*Am. J. Dis. Child.*, v. 68, p. 190, Sept., 1944.)

The fact that encopresis in children is, almost without exception, due to psychogenic factors is emphasized. Four case histories are presented in full and discussed. The author gives, as a basic cause, lack of parental love arising from the birth of a younger sister or brother who claims more of the parents' love, or from lack of a real home. The dictatorial manner of nagging parents may also cause encopresis by arousing either a feeling of revolt in the child, or a feeling that he is not loved. Change of environment, as when a child starts school, may also cause psychogenic incontinence until an adjustment has been made; a child just starting school interprets this environmental change as desertion by the mother. Other causes such as phobias are presented and discussed.

The author refers to the treatment of encopresis by pharmacologic and physical therapy as being "superfluous and non-specific; it works, if at all, by suggestion, by transference or if unpleasant by coercion, without resolving psychic conflicts and without improving the child's mental health."—R. L. Burdick.

LIVER AND GALLBLADDER

MCLEOD, K. W.: *An epidemic of common infectious jaundice.* (*J. Ped.*, v. 24, p. 454, April, 1944.)

The epidemic reported was concerned with 100 cases occurring in an institution for the feeble-minded over a period of 13 months. The patient group with the highest incidence was the idiot group representing 64%, next was the imbecile group with 40%, and finally the morons representing less than 2%. Of the entire population of 4,200 in the institute, only about 5% were ill. There were approximately a hundred people to each cottage-type building of the institute.

On the basis of age the greatest number of cases occurred in the groups between 10 and 24 years with the cases of the disease being more prevalent among the younger members. The static population confined to quarters had about 5 cases to every one case in the active group. The majority of the cases occurred during the fall and winter months. The clinical features were found to be quite constant. Following an account of the history, physical findings and laboratory studies, there is presented an excellent review of the literature on infectious jaundice. The conclusions reached were that the jaundice was a contagious disease, with an incubation period of a month, which was not necessarily conveyed by droplet infection.—George P. Blundell.

LESCIER, E. G.: *Nervous complications of infective hepatitis.* (British Med. J., p. 554, April 22, 1944.)

While nervous complications occur occasionally in spirochaetosis icterohemorrhagica, they seem to be even rarer in the epidemic form of infective hepatitis. This takes the form of meningitis in Weil's diseases. It may occur with or following the jaundice, and may even be the predominating symptom, the jaundice or hemorrhage being slight or even absent. The fluid is under increased pressure, pleocytosis is present, polymorphonuclear cells predominating in the graver cases and lymphocytes in the less severe. Spirochaets may be found in the fluid. Meningitis appears to be commoner in those cases without jaundice, consequently serological tests should be carried out in all cases of non-pyogenic meningitis in which the etiology is obscure. These nervous symptoms appear during the acute phase, although they may appear much later. Peripheral neuritis affecting the lower limbs has occurred as well as paralysis of some of the cranial nerves. In epidemic hepatitis, nervous complications are quite rare. Meningitis is here also the least uncommon nervous manifestation. Convulsions, hemiplegia, and mild polyneuritic signs may precede the onset of epidemic jaundice. Mental disturbances have been observed. Although there is a possibility that the occurrence of the two conditions is a coincidence, it is more likely that the hepatitis and the nervous complications are but two phases of the same disease.—H. N. Metzger.

SIMENDINGER, E. A.: *Thyroid function as a factor in gall-bladder disease and formation of gall stones; clinical and experimental study.* (Surg. Gyn., Obstet., v. 79, p. 10, July, 1944.)

An attempt has been made to determine clinically and experimentally whether a relationship between gall-bladder disease and hypothyroidism exists, since they both have aspects in common. Both are more common in middle aged females and are similarly associated with obesity. Also, high blood cholesterol levels are seen in both diseases. A large proportion of patients showed a low basal metabolic rate. In the thyroidectomized dogs, a high blood cholesterol occurred.

This did not result in an increase in the cholesterol output in the hepatic bile. The hepatic bile salt content and total biliary output were somewhat low as compared to the normal. The gall-bladder bile from these hypothyroid dogs showed a normal bile salt and cholesterol content in spite of an elevated blood cholesterol. When these hypothyroid dogs had their abdomens opened, it was found that the gall-bladders were greatly distended and contained much thick brown precipitate. In several dogs, many concretions were found. These concretions were composed of pigment, pigment soaps, and traces of cholesterol and calcium. Gall-bladders in thyroidectomized dogs showed a prolonged emptying time by cholecystography or failed to visualize. The conclusion is drawn that hypothyroidism does affect gall-bladder function. The large amount of debris and x-ray findings indicate that a marked degree of stasis exists in the gall-bladder. As a result of the impairment of function, the organ is rendered more liable to infection. This factor, plus the pigment concretions might readily precipitate the formation of stones.—H. N. Metzger.

LESCHER, F. GRAHAM: *The nervous complications of infective hepatitis.* (Brit. Med. Jour., v. 1944, p. 554, 1944.)

Hepatitis and nervous complications may not be a so uncommon combination as 2 phases of the same disease, and hepatitis should be looked for in all cases of infective nervous disease of doubtful etiology. Meningitis is the most common nervous complication in Weil's disease and in epidemic hepatitis. Diseases of the nervous parenchyma are rare in both infections. Cases of meningitis, of polyneuritis, and of hemiplegia presumably due to encephalitis, are described.—Courtesy Biological Abstracts.

MARTIN, E., MORSIER, G. AND ALPHONSE, P.: *Liver cirrhosis and the central nervous system.* (Helvetica Med. Acta, v. 11, p. 141, 1944.)

The cirrhosis of the first patient developed after an encephalitis (degenerative changes in putamen, diencephalon, hypothalamus), that of the second patient after a bicycle accident with head trauma (degeneration in the nuclei lentiformes and in hypothalamus, circular hemorrhages in the pedunculi). The relation between the lesions of the central nervous system and liver cirrhosis is discussed.—Courtesy Biological Abstract.

LI, TSAN-WEN, AND FREEMAN, S.: *The effect of bile salts on fatty liver production in dogs.* (Federation Proc., v. 3, p. 29, March, 1944).

Low-protein high-fat diets with or without a cholesterol supplement cause fatty livers in dogs but the degree of infiltration varies greatly. This may be due to poor fat absorption caused by an inadequate flow of bile into the intestine. Ten dogs were fed a protein-deficient high-fat (33 per cent) diet without cholesterol; 3 of these dogs also received 2.8 g. desic-

cated bile salts daily. Total fat from the fresh wet livers of the seven dogs without bile salts was 16.2 per cent; of the three dogs with bile salts was 19.1 per cent; cholesterol was 0.27 per cent and 0.40 per cent respectively. Thirteen dogs were fed the same diet with cholesterol; of these, three dogs also received 2.8 g. desiccated ox-bile salts daily. Total fat from the fresh wet livers of 10 dogs without bile salts was 26.3 per cent, on 3 dogs with bile salts was 31.2 per cent; cholesterol was 1.80 per cent and 1.76 per cent respectively. The decrease in dye clearance and elevating of serum phosphatase were not influenced much by added bile salts, nor was the degree of lipemia. The data suggest the per cent of fat in the liver is higher uniformly in animals fed bile salts. Lack of bile salt formation may be the reason for the small amount of fatty infiltration observed in some animals fed high protein and high fat diets.—E. R. Feaver.

DEANE, HELEN WENDLER: *A cytological study of the diurnal cycle of the liver of the mouse in relation to storage and secretion.* (*Anat. Rec.* 88 (1):39, 1944.)

Liver-cell organelles were studied in relation to bile acid secretion and storage of glycogen and fat in mice killed at 3-hour intervals during the 24-hour period, with uncontrolled and controlled feeding. Storage of glycogen occurs soon after eating; there is not always a correlative increase in cell size. Glycogen is laid down initially in the periphery of the lobule; during glycogenolysis, it disappears last from the center. Fat is sometimes deposited at the center after eating. No antagonism exists between the deposition of glycogen and fat. Bile acid secretion reaches its peak shortly before eating and is always most intense at the periphery of the lobule. There is no antagonism between the secretion of bile acids and the shortage of glycogen. There is no regular change in mitochondrial form in relation to the diurnal cycle. The Golgi substance lies more peripherally in the cell and is larger and more eosinophilic late in the 24-hour period. Both the mitochondria and the Golgi substance are larger at the periphery of the lobule than at the center. It is believed that neither of the organelles plays any role in the processes studied and that all zonation phenomena are a result of the nature of the blood supply.—Courtesy Biological Abstracts.

ULCER

MURLOCK, C. G.: *The present status of the treatment of uncomplicated duodenal ulcer* (*Proceed. Staff Meet. Mayo Clinic*, v. 19, p. 449, Sept. 6, 1944.)

Uncomplicated duodenal ulcer is primarily a problem for the medical therapist. Its treatment presents at present a major challenge to the medical profession since peptic ulcer probably is the chief disability of the present war. Providing complications are absent and other considerations warrant it, medical treatment should be given to 1) patients with ulcers present for a short time, 2) all patients under the age of 30,

3) older patients with mild symptoms, 4) patients with other conditions which would make surgery hazardous, 5) psychoneurotic patients without signs of hemorrhage, deep penetration or obstruction. The neurogenic factor is considered by the author the most important etiologic factor in many ulcer cases while the chemical factor ranks next in importance. Medical treatment is therefore based on the principle of controlling these factors. It is pointed out that there is no fixed program for hospital treatment; each case is attended to on its own findings and history. Diet-alkali therapy, antispasmodics, sedatives, and psychotherapy are important.—I. M. Theone.

THERAPEUTICS

JUNKER, W.: *Calcium in therapy of hyperacidity.* (*Therapic*, v. 17, p. 257, 1941.)

The most frequent cause of hyperacidity is vagotonia. Vagotonia is improved greatly if easily absorbed calcium is administered. In addition, the calcium also neutralizes the acid. Belladonna-calcium preparations to eliminate pain and reduce acidity were tried clinically with good results.—D. A. Wocker.

PERETS, L. G.: *Coli-therapy and coli-prophylaxis of bacillary dysentery.* (*Am. Rev. Soviet Med.*, v. 1, p. 458, June, 1944.)

Coli-therapy and coli-prophylaxis in dysentery depends for its action on what is termed "coli-antagonism". Coli-therapy has been practiced by a number of clinicians in a total of 1,318 cases reported. The treatment with coli-clotted milk has been administered safely with good therapeutic effect. Compared with control cases there has been observed a reduced mortality with a significant improvement in the course of illness and an earlier recovery. Results have been obtained proving coli-therapy to be at least the equal of sulfa therapy. The dosage is 50 to 100 cc. of coli-clotted milk given to acute dysentery cases three times a day on an empty stomach. Coli-prophylaxis appears to be of promise during an epidemic. It is recommended to eliminate the carrier state, and to avoid acute cases from becoming chronic. In one study there was no noticeable effect in children, while adults responded favorably.—G. P. Blundell.

GORDON, N. S.: *Treatment of infective hepatitis with glucose, insulin and ascorbic acid.* (*Brit. Med. Jour.*, v. 1944, p. 234, 1944.)

Treatment of 10 patients with 10 units of insulin twice daily, 25 mg. of ascorbic acid thrice daily and 5 g. of glucose spread over the day, was undertaken in comparison with 10 controls, both series receiving a fat-free diet and sodium sulfate. Average duration of the disease was 11.2 days as compared with the control average of 13.1 days, an insignificant difference. However, the improved clinical picture of the patients under treatment justifies the use in cases with severe symptoms, and where the insulin etc. is readily available.—Courtesy Biological Abstracts.

SURGERY

BAKER, J. W., AND EVOY, M. H.: *Incidence of common duct stones and post-operative management of the tube.* (*Northwest Med.*, v. 43, p. 137, May, 1944.)

The percentage of common duct stones varies proportionately with the number of ducts examined. Indications for exploration of the common duct are jaundice, repeated colic, chills and fever, recurrence of symptoms after cholecystectomy for stones, palpable stones in the duct, dilated ducts, contracted gall bladder, indurated pancreas, and gall bladder sand.

Surgical technique stresses opening of the duct, dilatation of the ampulla and management of the T-tube. Missed stones are suggested at the time of clamping the T-tube if colic occurs, or if a cholangiogram is positive for pathology if there is failure of the biliary sinus to close in 48 hours. Recurrent stones have symptoms or signs of biliary disease and may occur after a period of months.—Wm. J. Snape.

TURNER, G. G.: *Injuries to the main bile ducts.* (*The Lancet*, No. 6298, p. 621, May 13, 1944.)

Injuries to bile ducts are not rare but are serious when they do occur. One third of the patients die of the immediate consequences, one third die of the repair, and one third make good immediate recoveries but are liable to recurrent biliary tract disease which may be fatal. While anomalous ducts cause some accidents at operation, most are prevented by adequate exposure. The author prefers the Kocker incision. Immediate examination of the gall bladder after removal to demonstrate that only the cystic duct has been cut is very important, permitting immediate repair.

Immediate repair should be an end to anastomosis. Technical advice on locating several ends is given when repair is delayed. Pre- and post-operative care must be most scrupulous. Implantation of the stump into the duodenum is advised in the delayed repair.—Wm. D. Beamer.

NELSON, H.: *Early ambulation following section of anterior abdominal wall.* (*Ach. Surg.*, v. 49, p. 1, July, 1944.)

Analysis of observations on 426 personally conducted cases is presented. The patient's head is tilted upward as soon as the effects of the anesthesia are worn off. The patient then sits on the side of the bed, feet down and supported, and coughs and breathes deeply. He then resumes the recumbent position with head elevated. A short while later the patient walks with assistance to the bathroom and urinates. Intervals of rest are provided frequently and as required. Most of the patients walked within 24 hours of the operation. Complications were few. Contraindications to early ambulation must be strictly observed. Early post-operative ambulation has resulted in a low incidence of vomiting, nausea, abdominal distension, and pulmonary and cardiovascular complications. Bowel and bladder functions resume their normal course sooner and normal muscle tone also returns sooner. The acceleration in time of convalescence, the benefits to the

patient's morale and the reduction in cost of post-operative care are additional important advantages.—I. M. Theone.

TUJ, CO., WRIGHT, A. M., MULHOLLARD, J. H., CORABBA, V., BARCHOM, I., AND VINCI, V. J.: *(Sources of nitrogen loss postgastrectomy and effect of high amino acid and high caloric intake on convalescence.* (*Ann. Surg.*, v. 120, p. 99, July, 1944.)

Following gastrectomy patients usually experience a loss of body weight, a long period of post-operative debility and a decided negative nitrogen balance. The present authors fed a series of eight gastrectomy patients a high caloric diet with high concentrations of amino acids. Three other patients were given sufficient food to maintain nitrogen balance whilst eight patients were given the usual ward diets. The high-caloric amino acid group improved more rapidly, gained weight and the average post-operative time of bed confinement was cut in half. The starvation diet and continuous gastric suction usually employed are responsible for throwing the patient treated in the classic manner into negative nitrogen balance. Early administration of protein digests, such as amino acids, prevents this nitrogen imbalance and provides energy for bodily functions during the convalescent period.—G. Klenner.

EXPERIMENTAL MEDICINE

SECRETION

ROTH, A. J., AND IVY, A. C.: *The synergistic effect of caffeine upon histamine in relation to gastric secretion.* (*Am. J. Physiol.*, v. 142, p. 107, Aug., 1944.)

Using cats and humans, it was shown that the secretory response of the gastric glands to either histamine or alcohol is greatly increased by previous administration of caffeine. While caffeine itself acts as a gastric secretory stimulant, the synergism of histamine and caffeine or alcohol and caffeine may not be due to the secretory excitant properties of the caffeine. The gastric secretory response to histamine or alcohol and caffeine administered simultaneously is greater than the sum of effects from these drugs administered separately. The significance of these results to the peptic ulcer problem is discussed. While repeated histamine injections alone did not lead to changes in the gastric mucosa, a single dose of caffeine superimposed on the histamine injections led to bleeding, erosions, and ulcerations. The caffeine may provide a factor of "cellular toxicity" which lowers the resistance of the mucosal cells to damaging processes.—M. H. F. Friedman.

ABSORPTION

POPPER, H. AND VOLK, B. W.: *Absorption of vitamin A in the rat.* (*Arch. Path.*, v. 38, p. 71, Aug., 1944.)

Intestinal absorption of vitamin A was studied in the rat by means of fluorescence microscopy. When given in oily solution, vitamin A is absorbed like fat, the peak of absorption being the upper and middle thirds of the small intestine. There is reduction or absence of fluorescence in the lumen of the small intestine and at the

internal poles of epithelial cells. Absorption of vitamin A into the lacteals may take as long as 14 days. The authors suggest that this delay may be due to the fact that the mesenchymal cells, leukocytes or histiocytes which transport vitamin A to the lacteals may also store it for a time. There is disappearance of vitamin A fluorescence and of fat in the upper part of the small intestine. Two explanations for this are advanced.

Tocopherol was administered with vitamin A but showed no protective effects against vitamin A destruction. Atropine reduced absorption in the intestinal wall and increased vitamin A fluorescence in the intestinal contents. Neostigmine reacted oppositely by causing an increase in vitamin A fluorescence in the wall and decreasing it in the intestinal content.

The findings showed that the noneconomic utilization of vitamin A is probably caused by its destruction within the organism, particularly within the lumen of the intestine.—R. L. Burdick.

EXCRETION

TEGGIA, I. L.: *Alcohol excretion in the bile of normal persons.* (*Boll. soc. ital. biol. sper.*, V 17, P. 444, 1942.)

One hour after receiving 20 cc. of a 33 per cent solution of alcohol by vein the alcohol content of the blood is again within normal levels. The rates of decrease of blood and of bile alcohol do not run parallel. Bile alcohol reaches its maximum concentration 15 to 20 minutes after the intravenous injection and remains higher than the blood alcohol.

MISCELLANEOUS

DUNHAM, C. D., AND GILLESPIE, W. H.: *Diarrheal diseases in U. S. troops in Belgian Congo.* (*Bull. U. S. Army Med. Dept.*, No. 78, p. 76, July, 1944.)

This is an account of the sanitation measures taken to protect United States Army troops from diarrheal diseases, while they were stationed near a city in the Belgian Congo. The difficult period was in the first three months during which time the camp was under construction. Some of the measures included allowing natives to work only in the laundry, discontinuing the system of rotating kitchen police by roster, carrier state examination of food handlers, health education, and other special measures relating to personal hygiene. A bacteriological laboratory was considered necessary, and stress was placed on determining the source of infections because of the recognition that the incidence of dysentery was reduced by spending time on epidemiological investigation.—George P. Blundell.

PARKER, G. E.: *Retroperitoneal gas.* (*Lancet*, 6305, p. 5, July 1, 1944.)

Collections of retroperitoneal gas are rare, and in this report, four of the few possible causes are included in the five cases outlined. All five cases occurred in soldiers, four following gunshot wounds, and the fifth due to an accident. In the first case, the pelvic peritoneum was found to be elevated by a collection of gas, extending upwards between the leaves of the mesentery of the pelvic colon, and distending a number of ap-

pendices epiploicae, which had the appearance of small, gas-filled balloons. This was due to a large rent in the posterior rectal wall. In the second case, bubbles of gas and blood were seen under the peritoneum covering the outer side of the second portion of the duodenum. In this case the gas had gained entrance through two holes in the retroperitoneal portion of the duodenum. In the third case, the officer sustained a closed femoral fracture. Within a few hours the abdomen became distended and vomiting started. At autopsy, the retroperitoneal tissue was studded with gas bubbles and the leaves of the mesentery were separated by them. In this case, gas forming organisms entered the femoral wound and passed up through the femoral canal by way of the retroperitoneal lymphatics. In the fourth and fifth cases, entry was through the left thorax, posteriorly, at about the tenth interspace. The missile had passed forward through the diaphragm. In both these cases, a collection of air was seen stripping up the peritoneum on the abdominal surface of the diaphragm.—H. N. Metzger.

HEILMEYER, L. AND MUTIUS, V.: *Iron content of principle foodstuffs and iron recovery from food by gastric juice and bile.* (*Z. ges. exptl. Med.*, v. 112, p. 192, 1943.)

The ability of natural and artificial gastric juices to extract iron from foods was studied. Extraction and recovery of the iron proceeded equally well with gastric juice as with acid-pepsin solutions, while hydrochloric acid alone, of the same acidity as the acid-pepsin solutions, was superior. Optimum extraction with acid occurs at 140 millimols per liter concentration. Liver, bludwurst, spinach and sauerkraut yielded high iron values.—D. A. Wocker.

CANTAROW, A., PASCHKIS, K. E., RAKOFF, A. E., AND HANSEN, L. P.: *Solubility of certain steroids and other water-insoluble substances in aqueous solutions of sodium dehydrocholate.* (*Endocrinology*, v. 35, p. 129-131, August, 1944.)

A number of substances practically insoluble in water go into solution rather readily in aqueous solutions of sodium dehydrocholate. Among these are alpha-estradiol, estrone, estriol, progesterone, androsterone, testosterone, desoxycorticosterone, calciferol, diethylstilbestrol, methylstilbestrol, naphthalene and 2-methyl-1, 2-naphthoquinone. In the case of estrone, diffusion of a water-soluble estrogenic substance through cellophane suggests the presence of a rather firm estrone-dehydrocholate complex. The possible nature of this phenomenon is discussed and its practical usefulness suggested.—K. E. Paschkis.

VAN BRUCKE, F. AND GOLDBACH, H.: *Transport of oxygen through the gut.* (*Z. ges. exptl. Med.*, v. 3, p. 709, 1943.)

The oxygen saturation of portal vein blood could not be increased in dogs by either perfusing the intestine with oxygen or by introducing a saponin-gum-oxygen foam. Hydrogen peroxide perfusion also did not increase the oxygen content of the portal vein blood.

Hydrogen peroxide in 0.3 per cent concentration did not cause formation of gas emboli but did in 0.5 per cent concentration. Tissue damage due to gas emboli formation was responsible for the local effect of perhydral.—G. Klenner.

MANGIONE, G., AND GALEOTTI, G.: *The blood sugar curve of operated children after oral administration of glucose.* (*Boll. Soc. Ital. Biol. Sperim.*, v. 17, p. 344, 1942.)

Glucose (1.5 g./kg.) was given to 10 individuals of 1-10 years of age. Blood sugar determinations were made 30, 60, 120 and 240 minutes after the oral administration of the sugar. The experiment was repeated on the second, fourth and eighth day after operations for appendicitis or hernia. On the second post-operative day the blood sugar curve showed a slower rise, reached higher values and returned more slowly to normal level. On the fourth postoperative day the changes were less marked and on the eighth day the curve was the same as before operation.—Biological Abstracts.

RAWLINSON, W. A. AND KELLAWAY, C. H.: *Studies on tissue injury by heat. II. The liberation of enzymes from the perfused liver.* (*Australian J. Exp. Biol. Med. Sci.*, v. 22, p. 69, 1944.)

After about 7 hours perfusion of the isolated liver of the cat with saline at 38° C., histamine, inorganic phosphate, alkaline phosphates, catalase, esterase and proteolytic enzymes begin to appear in the persusate;

this is indicative of cell damage. The rapid increase in the rate of liberation of inorganic phosphate, alkaline phosphatase, esterase, proteolytic enzymes and to a lesser degree of histamine when the temperature approaches 40° to 42° C. is considered to be greater than can be accounted for by the normal exponential increase of the process operating at 38° C. The liberation of catalase and histamine just above 38° is slower than that of the other constituents studied; the liberation process for catalase satisfies the Arrhenius equation and it is, therefore, concluded that the rate-determining steps are characteristic of the enzyme. The gross deviation from the Arrhenius equation by alkaline phosphatase above 44° to 45° C. and by esterase above 45° to 46° demonstrate that irreversible heat inactivation is commencing. Catalase shows no such destruction up to 50° C.—Biological Abstract.

WELSH, J. H., AND HYDE, J. E.: *Acetylcholine content of the myenteric plexus and resistance to anoxia.* (*Proc. Soc. Exper. Biol. Med.*, v. 55, p. 256, 1944).

Experiments carried out on the longitudinal muscle and serosa of the entire small intestine of adult guinea pigs and rabbits showed that the acetylcholine content of the myenteric plexus is higher than any other mammalian nervous tissue. This high acetylcholine content of the myenteric plexus is believed to explain the proportionately greater resistance to anoxia and hypoglycemia. Likewise, the low resistance of the cortex and cerebellum is believed to be due to the low acetylcholine content of these regions.—R. L. Burdick.

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A Comparison of Gastric Acidity Among Men and Women Suffering From Duodenal Ulcer As Determined by Fractional Analysis of Gastric Contents After Injection of Histamine

By

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and

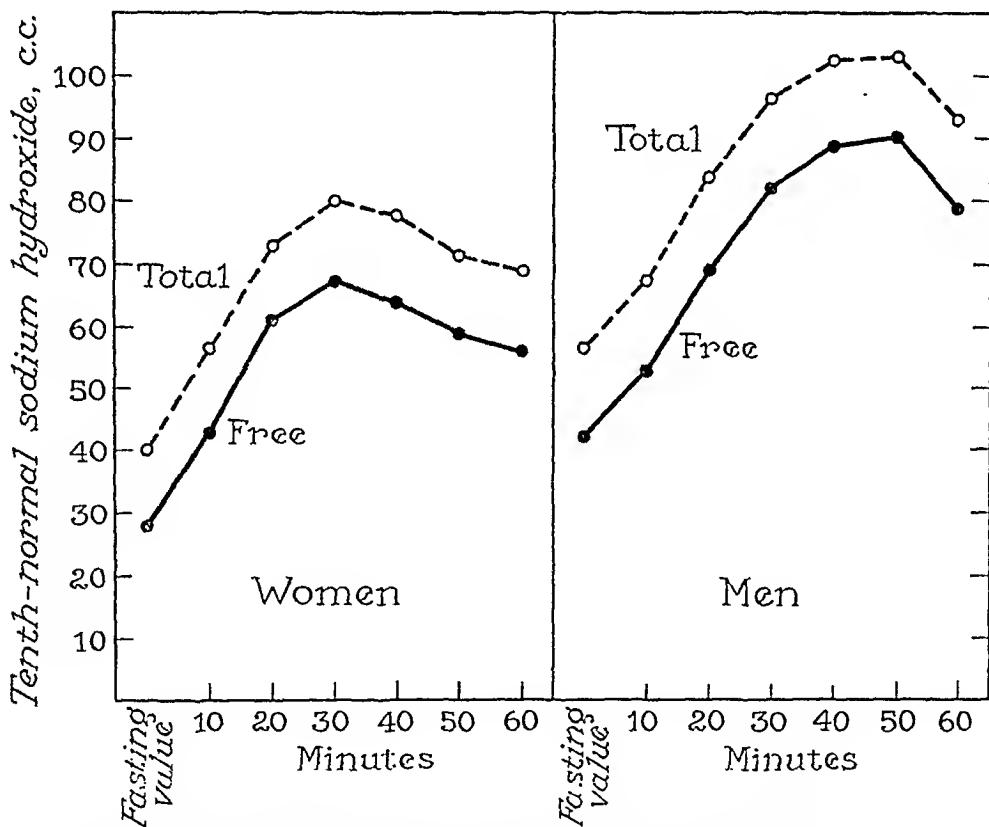
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THE greater incidence of duodenal ulcer among men than among women has long attracted much attention. Though much has been written on the subject, little is known as yet why this difference occurs. Most textbooks of medicine state that four times as many men as women suffer from duodenal ulcer, the records of the Mayo Clinic reveal our proportion to

to various conservative methods of treatment of ulcer.

We have noted in our work that the levels of gastric acidity as recorded for women were as a rule less than the levels recorded for men. The gastric acids play a major role in the causation of duodenal ulcer. Other factors that we consider important are the neurogenic element, the nutritional element, the infectious element



A comparison of gastric acidity among men and women suffering from duodenal ulcer as determined by fractional analyses of gastric contents after injection of histamine.

be nine to one while Miller (1) stated that among his patients in a southern state the ratio is more nearly twenty to one. Furthermore, when a woman does have an ulcer it is in most cases more readily responsive to treatment and less likely to recur than if the patient is a man. This study was made in order to determine what part the chemical factor might play in causing women to respond so much better than men

and the traumatic element. Of all the factors mentioned the neurogenic and the chemical phases are the most important. In this study we shall concern ourselves only with the latter.

We believe that one can evaluate the chemical factor most effectively by a study of the gastric acidity through fractional analysis of gastric contents after injection of histamine. The curve of acidity produced in this manner gives more information than a single specimen from the fasting stomach or a single specimen obtained

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TABLE I

The response of the gastric acids to the injection of histamine into women suffering from duodenal ulcer

Case	Fasting sample		Fractional specimens at 10 minute intervals											
			1		2		3		4		5		6	
	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid
1	10	20	20	32	20	30	42	58	40	56	40	58	30	44
2	30	42	40	58	44	60	70	84	70	86	70	88	80	92
3	0	16	32	40	56	64	58	68	48	56	38	50	50	68
4	76	88	40	50	54	66	100	110	116	130	102	114	98	108
5	6	20	0	8	50	64	68	80	60	78	80	94	64	82
6	48	60	48	66	60	78	98	112	100	120	100	116	110	128
7	22	34	58	68	68	78	50	60	32	42	32	40	20	36
8	38	48	58	68	64	76	42	52	56	68	50	60	46	56
9	40	60	60	80	84	98	100	116	100	118	60	78	60	76
10	30	48	46	60	60	74	60	76	80	94	100	112	80	96
11	0	16	18	32	50	60	64	72	50	42	26	32	20	30
12	32	42	30	44	90	100	78	90	66	76	64	72	54	68
13	6	20	26	40	40	52	58	76	70	88	82	94	84	98
14	0	10	30	44	50	66	10	28	70	82	94	106	104	120
15	46	60	66	80	80	94	80	98	42	50	24	36	34	46
16	20	36	32	42	42	56	40	52	26	36	12	18	12	20
17	44	60	40	52	40	56	70	84	70	86	42	56	40	54
18	20	34	30	46	48	60	70	84	80	92	92	110	74	88
19	12	26	10	20	30	42	70	84	70	86	58	70	80	94
20	48	60	68	82	72	86	78	88	46	56	56	66	50	62
21	0	6	0	10	0	8	36	48	64	78	60	72	38	50
22	0	6	0	10	20	34	24	36	30	44	30	42	16	34
23	30	48	26	40	50	64	70	84	58	70	60	76	58	70
24	0	10	48	60	64	80	70	84	40	56	20	32	10	20
25	10	20	20	34	40	54	60	76	80	94	80	92	60	76
26	36	46	62	76	82	92	80	92	86	96	84	98	82	98
27	50	64	66	78	82	94	74	84	84	96	42	50	46	52
28	38	48	74	86	96	108	70	80	70	80	58	68	54	64
29	30	42	70	82	88	98	82	94	40	54	24	40	52	65
30	58	70	60	76	70	84	78	90	70	84	70	78	76	88
31	30	38	90	100	84	92	76	84	52	70	42	56	22	34
32	16	24	34	66	102	112	90	100	64	76	40	52	44	54
33	38	52	86	96	100	108	90	98	72	80	66	74	58	70
34	50	64	80	88	92	100	104	112	104	120	92	102	82	92
35	50	66	48	60	50	64	50	64	66	80	74	90	80	96
Range	0-76	6-88	0-90	8-100	0-102	8-112	10-104	28-116	26-116	36-130	12-102	18-116	10-110	20-128
Mean	28	40	43	56	61	73	67	80	64	78	59	71	56	69

after administration of a test meal. Each patient was fasted for twelve hours preceding the study. The patient was placed at rest on his left side and a stomach tube was inserted in the usual manner. A specimen of the gastric contents was aspirated. Histamine was then injected subcutaneously in doses of 0.1 mg. per

kilogram of body weight. After this the contents of the stomach were removed at ten minute intervals. Each specimen obtained was titrated with tenth-normal sodium hydroxide. Toepfer's dimethyl reagent was used to determine the end point of the titration for free hydrochloric acid and phenolphthalein was used

TABLE II

The response of the gastric acids to the injection of histamine into men suffering from duodenal ulcer

Case	Fasting sample		Fractional specimens at 10 minute intervals											
			1		2		3		4		5		6	
Case	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid
36	48	62	52	68	50	66	80	94	80	96	98	110	70	88
37	58	72	50	66	70	80	80	92	90	104	100	112	80	92
38	30	44	40	52	64	80	80	96	90	104	80	92	80	94
39	38	60	58	74	80	92	100	112	100	114	90	104	58	70
40	0	8	5	22	16	22	20	36	24	34	18	28	0	6
41	26	38	36	48	70	88	90	106	98	110	84	100	70	82
42	0	6	0	8	30	42	44	58	54	68	70	84	60	78
43	30	42	60	74	60	78	40	52	30	44	60	72	60	70
44	60	78	80	98	76	90	84	100	80	92	90	106	60	80
45	0	6	0	8	18	28	30	42	70	80	80	94	60	76
46	58	74	76	90	98	110	112	124	110	122	120	134	118	128
47	30	42	40	50	74	90	94	110	96	110	94	108	66	80
48	58	70	40	58	54	66	70	86	104	116	120	134	54	70
49	60	76	80	98	80	100	104	118	112	124	110	122	120	132
50	100	112	94	110	100	114	110	120	108	122	120	134	90	110
51	60	78	66	80	84	96	90	106	90	108	92	110	60	80
52	40	60	60	76	80	98	100	114	100	112	98	110	80	96
53	30	42	48	60	50	66	78	96	80	98	80	100	70	88
54	52	70	54	70	80	98	106	120	110	124	104	120	100	114
55	60	78	80	96	80	96	98	112	100	116	100	114	104	118
56	50	66	48	60	70	84	90	102	98	110	100	112	100	110
57	26	40	30	48	54	68	60	74	66	80	34	50	36	52
58	44	60	50	66	60	78	70	82	84	96	80	94	84	96
59	44	58	60	72	80	94	80	96	98	112	100	116	80	96
60	20	32	26	48	30	42	40	56	64	80	76	88	56	70
61	40	54	52	66	70	84	90	106	98	112	100	116	90	102
62	16	28	34	50	50	66	58	70	60	74	76	90	80	94
63	80	98	110	120	120	138	120	138	120	136	104	120	102	120
64	94	102	108	116	122	132	124	136	126	136	126	132	128	140
65	22	26	54	62	82	94	88	98	66	76	100	108	122	130
66	30	44	30	42	44	60	60	78	80	96	80	98	50	66
67	50	64	60	74	76	88	90	106	110	124	110	128	112	128
68	40	54	50	64	80	96	100	110	110	122	88	98	80	96
69	30	44	70	84	90	102	98	108	102	114	84	96	88	96
70	60	74	60	76	90	104	100	112	110	120	70	84	80	92
Range	0-100	6-112	0-110	8-120	16-122	22-138	20-124	36-138	24-126	34-136	18-126	28-134	0-128	6-140
Mean	42	56	53	67	69	84	82	96	89	102	90	103	79	93

as the indicator to determine the end point of the titration for total acidity. Each value was recorded in terms of cubic centimeters of tenth-normal sodium hydroxide.

The results of analysis of gastric contents performed in the manner described were recorded for thirty-five

women and for thirty-five men who had been admitted to St. Mary's Hospital with the diagnosis of duodenal ulcer. These patients were not selected but were taken in order of admission. Tables 1 and 2 show the results of analysis of the gastric contents of these patients. The average value was determined for each

series for each fractional specimen. The averages were plotted as a curve and the curve as obtained from the women was compared with that obtained from the men (fig. 1.).

RESULTS

Higher values of gastric acidity and a more sustained volume were found for the men than for the women. The average maximal value of free hydrochloric acid was 90 c.c. of tenth-normal sodium hydroxide for the men and 67 c.c. of tenth-normal sodium hydroxide for the women. The average maximal values for total acidity were 103 and 80 c.c. of tenth-normal sodium hydroxide respectively.

Eight women had values for the free hydrochloric acid that equaled or exceeded 100 c.c. of tenth-normal sodium hydroxide while nineteen men had values equaling or exceeding this figure. Twelve women had total acidity equaling or exceeding 100 c.c. of tenth-normal sodium hydroxide while twenty-six men had values equaling or exceeding this level.

The women who had values of gastric acidity equaling or exceeding 100 c.c. of tenth-normal sodium hydroxide were found to be unusually nervous and high-strung, the so-called tension type. One of these patients (case 9) had a recurrent duodenal ulcer and her response to treatment was slow and appeared to be

more of the "male type" than the usual response of women.

The marked difference of the chemical factor in these two series of patients seems to explain, at least in part, why women suffering from peptic ulcer respond so much more satisfactorily than men to conservative types of ulcer therapy.

SUMMARY

A comparison of the gastric acidity of men and women suffering from duodenal ulcer shows that the male patients have much higher values than the female patients for free hydrochloric acid and total acid in response to the injection of histamine. The incidence of very high values, that is, equaling or exceeding 100 c.c. of tenth-normal sodium hydroxide, is greater for the series of male patients than it is for the female patients. The higher incidence of hyperacidity among the men may help to explain the greater tendency to intractability of duodenal ulcer among men. The gastric acidity of women suffering from peptic ulcer is usually not abnormal. Neurogenic causes, on the other hand, are usually very apparent among women who have duodenal ulcer. The utilization of this information is obviously clinically important in determining the type and intensity of treatment of duodenal ulcer.

REFERENCE

- Miller, Tate: Personal communication to the authors.

The Use of Naturally Carbonated Saline-Alkaline Mineral Waters in Conditions Affecting the Alimentary Tract

By

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SARATOGA SPRINGS, N. Y.

I. INTRODUCTION

The treatment of conditions affecting the alimentary system by the use of mineral waters has a long traditional background. The patient with stomach disorders has for centuries gone to Kissingen, Harrogate or Montecatini, while the patient with liver and gall-bladder conditions has traveled to Karlshad or Vichy to utilize their natural mineral waters. These are only a few examples of the hundreds of spas where these conditions have been treated.

In this country the naturally alkaline saline waters of the Saratoga Spa have been used for these ailments for the past 175 years. Many eminent physicians have reported on their value.

II. LITERATURE

In reviewing the earlier writings on the use of mineral waters at Saratoga, one is impressed by the en-

thusiastic reports. They must be interpreted with an insight to the medical knowledge of the time.

Dr. Samuel Tenney, in a letter written in 1783, which was published about ten years later (1), reported his studies of the mineral waters and the clinical results. He stated, "I had afterwards two patients, whose livers were left greatly tumefied, indurated, and painful, by an obstinate jaundice; in which the common deobstruents had little or no effect. I sent them to the springs for relief; and within a week they returned perfectly cured." Another patient "with a tetterous eruption" and an associated disturbance of stomach and bowels was sent to the springs and the doctor wrote, "After using the acidulous waters for twelve or fifteen days, he returned to quarters surprisingly reduced: complaining that 'They had torn his stomach all to pieces'". In comment, Dr. Tenney said, "I apprehend that he used the waters imprudently, and that if he had made a judicious use of the two different kinds (acidulous and chalybeate), he might have found the assistance from them, which he had in vain sought from other medicines." He concluded

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" . . . that the acidulous waters possess considerable aperient or deobstruent powers, and may, therefore, be useful in most kinds of obstructions", and, "The chalybeate water may, without doubt, be an excellent remedy in all cases of simple relaxation."

Seaman in 1793 (2) reported his analysis of the waters at Saratoga and added some comments on their medical virtues which were apparently verbal reports to him. He stated, "I fully believe according to the accounts of the neighbors, and persons who had experienced relief from those complaints, that they may be serviceable in *chronic rheumatismus*, *dyspepsia*, and some other long standing complaints of debility." Again, "From the conjoined effects of purgative antiseptic and tonic qualities; they appear to be properly formed for the cure of the dysentery". Also, "Their use in *hypochondriasis* and other *nervous affections* . . . perhaps depend in a great degree upon amusing scenes, more simple food, and constant exercise". In another field, to digress, it is interesting to note a contraindication which has continued to the present. To quote, "Fixed air which seems to be the predominant agent in the operation of these waters, has, by those who have made experiments thereon, generally been found prejudicial in these complaints (consumptions). in fact the common report is, that these waters are prejudicial in phthisical complaints."

In a later report, 1809, Seaman (3) enlarged on some of the effects of the waters; "Their operation upon the bowels may pretty certainly be calculated upon, if taken before breakfast; if not taken until afterwards, they more generally affect the other excretions." Regarding their use in *dyspepsias* he stated, "The carbonic acid furnishes the cordial exhilarating stimulus, the salt promotes digestion, while the iron restores the lost tone of the enervated stomach: at the same time the soda corrects the acidity so often predominating, and the whole composition, when judiciously managed, obviates that costiveness, so frequently an aggravating attendant upon them."

Meade in 1817 (4) wrote regarding the waters, "I should conceive that they were of little value indeed, if they were not capable of doing great mischief;" "The first class of diseases which are peculiarly benefited by the use of these springs, are those which proceed from a disordered state of the alimentary canal, or from obstructions of any of the viscera particularly of the biliary organs, whether occasioned by irregularity in living, or the vicissitudes of climates or season. This comprehends a great variety of diseases, which are generally and fashionably called *Bilious*." This author outlined a program of taking the waters and stressed the ill-effects of their excessive and indiscriminate ingestion. He advised the regulated use of chalybeate waters for *dyspepsia*. He also recognized the value of a sensible diet, regular exercise and proper physical and mental rest in addition to the use of the waters.

From 1817 to 1838 the writings of Steel (5) which appeared in six different printings described the waters and their use. To quote from his first edition, "Among the great variety of invalids who resort to the Springs,

none, perhaps, receive more essential and effectual benefit from their use, than the *Bilious and Dyspeptic*." In these disorders he recommended the laxative waters and for the dyspeptic also the chalybeate waters. He also noted the danger of too much water and the need in some patients of some additional laxative drug at the beginning. He mentioned the bathing program as supplemental to the internal use of the waters.

In Steele's 1831 edition appeared the following, "In the more advanced stages of bilious affections, where the organization of the liver and other viscera have materially suffered, and the disposition to general hydrops, indicated by the enlargement of the extremities, fullness of the abdomen, etc., the waters are all of them manifestly injurious, and are not to be admitted, even as an auxiliary remedy." He also expressed a doubt of the value of chalybeate medicines as *tonics*, "It is certain that three-fourths of the cases usually termed *dyspeptic*, which congregate at these springs during the drinking season, owe their origin to the ill-timed administration of chalybeates and other *tonic* remedies, prescribed for the purpose of bracing up what was supposed to be a debilitated stomach;". He still spoke of the stimulative effect of these waters but felt that the iron present was not sufficient to effect this result. He also recognized the presence of iodine and bromine in the waters, elements which had only been discovered a few years before.

The doctors who prescribed these waters a century ago referred to their effects as aperient, diuretic, deobstruent, alterative and tonic (North 1840) (6). It was earlier thought that the stimulating or tonic effect depended on the chalybeate (iron) content of the water but to quote North, "There is no exception to the fact, that whether iron be present or absent, an internal use of these remedies is productive of stimulating and tonic effects."

From the clinical observations and from the chemical analyses of the waters North, in 1858. (7) stated, "Under the guidance of both these tests we are authorized to say that these waters are 1st, laxative or aperient; 2nd, diuretic; 3rd, antacid; 4th, deobstruent; 5th, alterative; and 6th, tonic."

Allen in 1848 (8) wrote with reference to bilious diseases, "In those cases where the liver is making bile improper in quality or quantity, and without organic lesions in the viscus, these waters used as a cathartic in the morning, with such assistants over night as the case may require, produce the most happy results." With reference to the alterative use of the waters he said that it was necessary for the water to enter into the system proper. To quote, "This is only to be done by small potations taken repeatedly through the day; and in most instances these drafts should be taken from the more tonic fountains of the Village."

Later Bell (9), in 1855, wrote, "The feeling of load and oppression in the abdomen, sometimes resulting from undue retention of food in the stomach, sometimes from enlarged liver or spleen, sometimes from fecal accumulation in the large intestine, and again from flatus and distention in different parts of the cecal, often from sluggish circulation of the portal sys-

tem, all of which derangements of function may manifest themselves at the same time, will be relieved in the same way, viz: by free secretory action of the mucous membranes of the intestinal canal procured by the purging springs of Saratoga. The disorders of the abdominal viscera here noticed, pass by the various names of *dyspepsia*, *liver disease*, *bilious complaints*, *costiveness*, *piles*, etc." He considered the main effects of the waters were aperient and alterative.

The indications for the waters as given by Walton in 1874 (10) include *dyspepsia*, *jaundice* depending on catarrh of the biliary ducts, *gall-stones* and *engorgement of the liver*. He gave the following suggestions for their use, "For a cathartic effect, drink two or three glasses leisurely, before breakfast, then walk for ten or fifteen minutes, and take another glass or two; breakfast half an hour afterward. As an alternative take a glass three or four times a day." As the iron content of the waters varied, he advised a smaller alterative dose for the waters with the greater amounts of iron.

As evidence of changing medical thought, Irwin, in 1892 (11) after giving a chemical classification of the waters at Saratoga, wrote "and finally according to their therapeutic effects, as *laxative*, *aperient*, *cathartic*, *diuretic*, *alterative*, *anti-lithic*, *tonic* and *strengthening*. But all of these divisions (chemical and therapeutic) are unsatisfactory and misleading." In discussing the effect of the waters on metabolism, he wrote, "An *alternative* is a medication or an influence, which without purgation, diuresis, or other noticeable excess of secretion, or antecedent phenomena of any kind, restores to its normal condition the disordered process of metabolism. It is mainly because of their alterative quality, that the Saratoga waters are so superlatively valuable in almost every form of chronic disease—in all of an indolent character. It is equally, because of their stimulating influence upon metabolism, that they are usually contraindicated in malignant, wasting, or inflammatory ailments." The writer stated his conception of the way mineral waters produce effects as follows, "Mineral waters seldom act directly as specifics for diseases, but rather as the correctives of the constitutional conditions which give rise to and maintain it." In the field of gastrointestinal disorders this author in accord with those quoted above suggested the use of the waters for patients with *dyspepsia*, *liver congestions* including general torpidity and biliousness, *constipation* and *abdominal plethora*.

Other terms creep into use such as Burchard applied in 1892 (12), "The physiological effects of mineral waters may be considered as *tonic*, *alterative*, *reconstructive* and *depurative*." He stressed their use in chronic conditions and the fact that the mineral waters will, in addition to mechanically clearing the intestinal tract, also through influence on capillary circulation bring about beneficial changes in the cells of the body. He suggested their use in *gastric* and *intestinal catarrh*, *dyspepsia*, *chronic constipation* and *functional hepatic derangements*.

Ferris (13) in 1915 states, "They are used—according to the choice made by the physician, and accord-

ing to the patient's necessities—in digestive disorders, especially *intestinal stasis*, inactivity of the liver and flatulence".

Moriarta in 1920 (14) described their effects as follows: "When taken internally our mineral waters exhibit two distinct qualities which I characterize as their *immediate* and *remote* action. The *immediate* effect is to clean out the intestinal tract and stimulate the natural secretions of the mucous glands. . . . The *remote* action is found in the correcting of perverted metabolism, of anemia, and many ill-defined morbid conditions of a more or less chronic nature."

In 1934 McClellan (15) stressed the physiologic as well as the clinical approach in a review of the use of the mineral waters in liver and gallbladder conditions. He stated, "I would point out the need for very careful clinical and laboratory observations dealing with the use of mineral waters in order to establish very definite indications for their use."

Again in 1941, Yunich (16), in discussing functional gastrointestinal disorders, stressed as causal factors an inadequate constitution, autonomic imbalance, and psychic stress. He pointed out the value of relaxation, both mental and physical, for these patients such as can be provided at a well organized and controlled spa where exercise, rest and recreation are combined with an adequate program built up around the use of the mineral waters.

In a recent survey of the medical work of The Spa, the writer (17) found that approximately 22,000 patients with gastrointestinal ailments have been cared for during the past ten years. This number represents 17.6 per cent of the estimated 125,000 patients treated at The Spa for this period. This finding emphasizes the importance of careful evaluation of the saline-alkaline waters in ailments of the gastrointestinal tract.

III. Physiologic Considerations

In the application of any type of mineral water to disturbances of the gastrointestinal tract it is important to consider both the pathologic physiology of the tract and the physiologic influence which may result from the use of the waters.

The changes which may occur in secretion and motility as a result of the disturbed nervous impulses are well known. Whether the impulses are initiated by physical disease in other body systems or by psychic disturbance, they will initiate symptoms of disorders in the digestive tract.

Congestion, which may be defined as an abnormal amount of blood in the vessels of an organ or tissue, may occur as a result of conditions directly related to the intestinal tract such as poisoning, intoxication, and inflammation. It is also present in the chronic passive congestion of cardiac and renal disease.

The principal physiologic disturbances, whether they are produced from distant causes or from local irritations, are changes in the volume and constitution of the various digestive secretions and alterations in the motility of the tract. The details of these changes are well known to physicians who practice gastroenterology and will not be elaborated further in this presentation.

It is necessary, however, to give consideration to the nature of the mineral waters used and to outline the ways in which they may produce changes in the pathologic physiology of the intestinal tract. The waters of The Saratoga Spa are all naturally carbonated, containing from two to four volumes of gas to every volume of water as they come from the ground. The principal mineral constituents are the chlorides of sodium and potassium and the bicarbonates of calcium, magnesium, sodium and iron. In addition they contain smaller amounts of the elements which are spoken of today as "trace elements". The waters, because of their carbon dioxide content, are slightly acid and show pH of 6.4 to 6.8 as they come from the ground. The Hathorn No. 2 water contains 15.8 gms. of mineral constituents per liter, the Coesa, 11.6 gms., and the Geyser 7.3 gms. These waters are characteristic of the three groups of mineral waters found at The Spa.

The way in which these waters may influence physiologic function will be considered under three headings: first, temperature; second, mechanical; third, chemical. The first two considerations, those of temperature and mechanical influences are more important in the external use of the waters than in their internal consumption. However, the temperature at which the fluid is taken will influence to some extent the peristaltic response and, therefore, the motility of the stomach and intestinal tract. When taken internally, the chemical constituents of the waters must have principal consideration.

The influence of carbon dioxide on the mucous membranes of the mouth, esophagus and stomach, likely will be similar to that occurring when the skin is exposed to water containing this gas. There is an increase in the number and the diameter of the capillaries in the skin. For many people waters containing carbon dioxide are definitely more palatable than is plain water itself. In a relatively small percentage of people the carbon dioxide may act as a disturbing factor, increasing the gas and discomfort from which they suffer.

When waters containing carbon dioxide come in contact with the gastric juice in the stomach, or with the secretions in the intestinal tract, the gas which is present in the free or partially bound state will be released. It is then eliminated from the body either by the blood stream and lungs or by belching. The further chemical effect of the waters will then depend on the remaining minerals and the tonicity as related to blood serum.

In the waters at The Saratoga Spa three groups of minerals may be considered, the salines, the bicarbonates and the "trace elements". It is, of course, important to realize that combinations of minerals may produce different physiologic effects from those noted when a single constituent is studied by itself. The studies on the influence of salines on the secretions of the gastrointestinal tract have shown that a decrease in the intake of sodium chloride may result in the diminution of the amount of acid in the gastric juice. An adequate supply of sodium chloride is required for a normal secretion of hydrochloric acid. The saline waters are clinically of value in the relief of many

symptoms associated with mucous gastritis. It is suggested from this fact that the salines, or possibly the bicarbonates in these waters may play a direct role either in making the natural mucous secretion of the stomach more liquid or in mechanically removing it from the wall of the stomach when it is present in excess amounts.

Further effects of the minerals in the waters come as a result of their absorption into the blood. Here by an increase in the bases such as sodium, calcium and magnesium, the alkaline reserve of the body is built up. The part played by these minerals in liver physiology requires further study. As previously pointed out in the older records, these waters were used extensively in patients with "bilious" conditions, and the statement was made from time to time that they increased the amount of bile secretion. The writer is not familiar with any detailed studies to support this statement. The investigations of Weiss (18) suggested that the use of the Coesa water would result in better gallbladder drainage. He studied only a small number of patients with duodenal drainage at the beginning of treatment with the mineral waters and again at the end of the two or three week period and found that the "B" fraction of bile was less concentrated at the end of treatment.

The effect through their influence on the motility of the intestinal tract is primarily laxative. When the stronger saline waters, such as the Hathorn No. 2, and in some patients the Coesa, are taken in the morning before breakfast, in amounts of 250 to 500 cc. (one-half to one pint), elimination will frequently follow within one to two hours. If increased amounts of the waters are taken, then the elimination may be more rapid and they act more as a purge. Physiologically, the increased intestinal motility is dependent on the presence of considerable amounts of magnesium bicarbonate and also on the fact that these waters are somewhat hypertonic when compared with concentration of the blood serum. The carbon dioxide which is released from the waters in the intestinal tract may act as an additional stimulant to muscular activity.

Further physiologic influences of the waters may result from the effect of the minerals on the glandular and nervous systems of the body, inasmuch as these two systems both play an important part in gastrointestinal physiology. The minerals contained in the waters, even those present in small amounts, are similar in nature to the minerals which act as catalysts in a number of the enzyme systems of the body (19). Further study of these mechanisms may provide data to support the older belief in the *alterative* effect of these mineral waters. The concept of those writing about the waters in the past century which suggested their influence on metabolism and cellular activity may find definite physiologic explanation in the mineral-catalase-enzyme systems which are being studied so carefully today.

IV. CLINICAL CONSIDERATIONS

It does not seem necessary in this presentation to list each clinical condition of a gastrointestinal nature in order that the reader may establish indications for

the use of the waters. The above physiological consideration has pointed out the ways in which waters may influence pathologic physiology of the intestinal tract.

Many of the disturbances in the intestinal tract are manifestations of abnormalities elsewhere, particularly in the nervous or glandular system of the body. It would not be satisfactory to treat these conditions without recognizing their nature and making every effort to correct the underlying disturbance which is present. To say that mineral waters will correct psychic trauma is far-fetched. However, psychic trauma will produce pathologic physiology in the gastrointestinal tract which results in disturbed secretion and disturbed motility. The waters may, as pointed out above, influence these factors and so may be used by many patients of this type with real benefit.

All throughout the writings of the past century and a half, quoted above, the term *dyspepsia* is mentioned as a condition in which the waters are of value. *Dyspepsia* is discussed today under the titles "gastric neurosis" and "functional gastrointestinal disorders." In many of these patients elimination is poor and changes in the secretory activity of the digestive glands occur. Experience has shown that the naturally carbonated saline-alkaline waters can produce beneficial clinical response, particularly in those patients where either or both the secretory and the mechanical activity of the intestinal tract is below normal. Since the waters are stimulating they should be used with caution by patients with hyperacidity or functional diarrhea. In this group of patients waters containing the basic alkaline minerals will be of benefit if properly administered.

In order to obtain the greater stimulating effect on secretion and motility, it is necessary for the physician to prescribe the waters during the period when the stomach is without food. It has been shown in this connection that the use of bicarbonate of soda on an empty stomach will stimulate greater production of acid and therefore its use to neutralize excess acid secretion of the stomach has been disappointing. In order to obtain a greater influence from the alkaline salts in these waters they are best taken within one or two hours after meals while food is still in the stomach. To reduce the stimulating effect of the carbon dioxide gas the water may be exposed to the air, or mechanically stirred with a spoon to dispel some of the carbon dioxide. The amounts and the time when the waters should be taken must be planned by the physician in charge of the patient's treatment.

Gastritis received much attention in the older literature. In patients with excessive mucous secretion, (catarrhal gastritis) it is sometimes found that the secretion of hydrochloric acid and the digestive enzyme,—pepsin,—may be somewhat below normal level. Its association also with poor hygiene, irregular eating habits, and the consumption of abnormal combinations of food has been pointed out. In this condition the regular use of the waters described above has been beneficial. It must be emphasized that both here and in functional gastrointestinal disorders, the correction of the underlying difficulty is the principal goal of the physician when treating patients.

In patients with *peptic ulcer* or *malignant condition* of the stomach, the waters should be used with extreme care. They may increase the hemorrhage which frequently complicates both of these conditions. Whether this is due to the influence of the waters in producing greater capillary circulation in the wall of the stomach or whether increased peristaltic activity may dislodge the clot or thrombus which may have controlled the bleeding in the ulcerated area, is not known. In the patient with chronic ulcer discriminate and controlled use of the waters for their alkalizing properties can be followed with safety under the doctor's direction.

Among the disturbances in the intestinal tract, *colitis* and *constipation* often are found. In colitis where frequent watery stools are present, there is a definite loss of minerals from the body. The use of the waters containing sodium will help to prevent the development of dehydration, which in patients with colitis may be of serious consequence. They must be taken in amounts of from 100 to 250 cc. at relatively frequent intervals through the day in order to avoid the laxative effect from their use.

In patients with *constipation* where it is the result of poor dietary habits or where weakness of the muscles of the intestinal tract is present, the waters may be taken with definite benefit. As indicated above, the best results follow the use of approximately 250 to 500 cc. taken in the morning before breakfast on an empty stomach. In some patients the waters may not be sufficiently laxative to meet their requirements. Then, it is advisable for the physician to use some additional laxative preparation, or possibly prescribe the use of one or two colonic irrigations following which the waters may be found sufficient to produce regular elimination.

In the field of *liver* and *gallbladder disturbances* experience has shown that many patients will obtain definite symptomatic improvement during and following a regular period when they use these waters. The condition frequently described as *liver congestion* is, of course, difficult to diagnose clinically. It may be produced by disturbed conditions in the gastrointestinal tract itself or by the congestion which may complicate renal disability. Beneficial effects of the waters in patients with active congestion will result from the improved elimination through the intestinal tract and the more natural handling of foodstuffs which follows the improved secretory activity.

In *gallbladder disease*, either with or without the formation of gallstones, the use of the waters has resulted in definite relief of the symptoms and as pointed out in the work of Weiss, there is a suggestion that the bile which is stored in the gallbladder may be less concentrated and more frequently emptied during the course of treatment with the mineral waters. Here the waters are more effective when taken from one to two hours before meals when the stomach is empty. For patients who have had their gallbladder removed, the physician can use the mineral waters and other treatments in their program of convalescent care.

In summarizing the place of the mineral water treatment in diseases of the gastrointestinal tract, the

changes discussed are primarily the result of the internal use of the mineral waters. In the program of treatment at The Spa, their application in the form of baths is an almost constant corollary. In this way the physician directing the patient with a gastrointestinal disorder may accomplish much in allaying or reducing the psychic factors which are recognized as important in the initiation of disturbances in this system of the body. The use of the mineral waters internally is only a part of the program. The goal of the treatment in Spa Therapy is improvement in the patient even more than the treatment of a disease entity.

In the field of chronic disease where the use of mineral waters and Spa treatment has been found beneficial, their influence on the natural building up and breaking down processes called "metabolism," is important. The ingestion of mineral waters provides one of the vital body building stones, namely, minerals. As suggested above, the important part played by minerals in the catalytic and enzyme systems is now recognized. It is possible for widespread disturbances to be initiated when any factor in these systems may be deficient.

It is clear from this discussion that many controlled physiologic and clinical studies must be made before one can explain the beneficial effects observed when these mineral waters are used by patients with disturbances of the gastrointestinal tract.

V. CONTRAINDICATIONS

There are definite contraindications to the use of these mineral waters which should be noted. Comment has been made on their application in patients with *ulcer* or *carcinoma* affecting the stomach and intestinal tract. Also, in any condition where hemorrhage is or may be a complication, their use should be guarded. If mechanical obstruction of the intestinal tract is present, the use of the mineral waters should be withheld until the obstruction has been removed. In acute abdominal disorders such as *acute appendicitis*, *perforation*, or *acute pancreatitis*, the waters should not be used as a laxative. In *chronic passive congestion* of the liver, spleen and other organs of the abdominal cavity, depending on cardiac and renal disease, the waters should be used with caution because edema is a frequent complicating condition which may be accentuated by an increased intake of sodium. Sodium is present in the natural waters of Saratoga in considerable quantity. Therefore, their use in any condition with latent or chronic edema must be discouraged.

In treating conditions of the gastrointestinal tract, one should consider other disturbances which may be present. One of these may be pulmonary tuberculosis. In this condition, physicians as far back as 1800 advised against the use of these waters. They found patients with active pulmonary tuberculosis usually did poorly when they were taken. They believed that the stimulating effect of the mineral waters on metabolism was harmful in patients where metabolic activity was already above the normal level, particularly in the phase of infection and fever. Observations in recent

years appear to support this opinion particularly in relation to tuberculosis and active infections.

VI. GENERAL CONDITIONS

The newer studies on the physiology of the gastrointestinal tract including the liver and gallbladder are leading to a more rational therapeutic program in the treatment of conditions affecting this system. There is yet, however, room for further study. A review of the historical backgrounds of diseased processes is of interest as it shows the change in emphasis as increased knowledge regarding the condition is uncovered. In the literature quoted above, one finds the terms "tonic", "alterative", "aperient", and "laxative" being frequently used. The modern physician looks on these terms as scrapbooks and feels that they have no sound basis for use today. It is interesting to point out that the term "alterative" as used in the writings of the old physicians may have a modern counterpart in the mineral-catalytic-enzyme systems which are receiving so much attention today. The terms "aperient" and "laxative" have now been replaced largely by the expression "improved elimination through the intestinal tract," although the term "laxative" is freely used in medical writing today. Many people feel that the term "tonic" has been misused. This, no doubt, is true. But it can be used to describe improved functioning particularly of the mechanical systems of the body. Certainly we recognize in the field of muscle physiology that some treatments will result in greater contractile power. If this can be translated into the individual as a whole, then stimulating or tonic changes must be recognized.

The interpretation of the writings of the past 150 years in relation to the mineral waters must be made on the basis of the medical knowledge of the times. The newer biochemical and physiologic medicine is finding that the empirical indications as outlined by the older physicians may have definite experimental explanation as new tools are applied in the study of disease.

CONCLUSIONS

1. Disturbed physiology of the gastrointestinal tract is manifest primarily in abnormal secretion and abnormal motility.
2. Congestion of the organs may result either from disturbances in the tract itself or from causes outside such as cardiac and renal diseases.
3. The nervous control of gastrointestinal function is recognized as a pathway through which physical and mental stress may produce both symptoms and physical disease.
4. The application of mineral waters in the treatment of these conditions is based upon their influence on secretion and motility of the intestinal tract.
5. The part they may play in cellular metabolism is discussed but it must await further study for clarification.
6. Their use has been generally beneficial in conditions where either secretion or motility, or both, is below normal. Their use should be carefully controlled

when the secretion and motility are above normal as found in functional conditions of hyperacidity, diarrhea or peptic ulcer. Also where chronic passive congestion, dependent on cardiac and renal conditions, is present, the mineral waters should be used with great caution.

REFERENCES

1. Tenney, Samuel: An Account of a Number of Medicinal Springs at Saratoga, in the State of Newyork; Memoirs of the American Academy of Arts and Sciences, vol. ii, part i, pp. 43-61, Boston 1793.
2. Seaman, Valentine: A Dissertation on the Mineral Waters of Saratoga. New-York. Samuel Campbell. 173. pages 33 and 34.
3. Seaman, Valentine: A Dissertation on the Waters of Saratoga, including an Account of the Waters of Ballston. New-York. Collins & Perkins. 1809. pages 87 and 92.
4. Meade, William: An Experimental Enquiry into the Chemical Properties and Medicinal Qualities of the Principal Mineral Waters of Ballston and Saratoga, in the State of New-York. Harrison Hall, Publisher. William Fry, Printer. 1817. pages 110 and 119.
5. Steel, John H.: An Analysis of the Mineral Waters of Saratoga and Ballston, with practical remarks on their use in Various Diseases. First Edition. 1817. page 81.
- Steel, John H.: An Analysis of the Mineral Waters of Saratoga and Ballston, with Practical Remarks on their Medical Properties. Saratoga Springs. G. M. Davison. 1831. pages 186 and 189.
6. North, M. L.: Saratoga Waters, or the Invalid at Saratoga. New York. M. W. Dodd. 1840. page 21.
7. North, M. L.: Analysis of Saratoga Waters; Also, of Sharon, Avon, Virginia, and other Mineral Waters of the United States. Saratoga Springs. B. Huling. 1858. page 23.
8. Allen, R. L.: A Historical Chemical and Therapeutical Analysis of the Principal Mineral Fountains at Saratoga Springs; Together with General Directions for Their Use. Saratoga Springs. B. Huling. 1848. pages 61 and 64.
9. Bell, John: The Mineral and Thermal Springs of the United States and Canada. Philadelphia. Parry and McMillan. 1855. pages 78 and 79.
10. Walton, George E.: The Mineral Springs of the United States and Canada, with Analyses and Notes on the Prominent Spas of Europe, and a List of Sea-side Resorts. New York. D. Appleton and Company. 1873. page 175.
11. Irwin, J. A.: Hydrotherapy at Saratoga, A Treatise on Natural Mineral Waters. New York. Cassell Publishing Company. 1892. pages 75-76, and 80.
12. Burchard, Thos. H.: The Saratoga Mineral Waters. A Clinical Essay. New York. 1892. page 25.
13. Ferris, Albert Warren: The State of New York Develops an American Spa; The Modern Hospital, Vol. V, No. 6. December, 1915.
14. Moriarta, Douglas C.: Practical Side of Saratoga Springs as a Health Resort; Albany Medical Annals, October 1920.
15. McClellan, Walter S.: Hydrotherapeutic Measures in Hepatic, Gallbladder and Biliary Tract Diseases; Review of Gastroenterology, I, 104, (June) 1934.
16. Yunich, Albert M.: Functional Gastrointestinal Disorders and their Management; presented at a Round Table Discussion before the meeting of the Medical Executive Committee of the Saratoga Spa, Saratoga Springs, N. Y., May 21, 1941.
17. McClellan, Walter S.: New Trends in the Treatment of Chronic Disease: An Experience in Spa Therapy; Annals of Internal Medicine, 18, 825, (May) 1943.
18. Weiss, Moses: Personal communication.
19. Baudisch, Oskar: Magic and Science of Natural Healing Waters; Journal of Chemical Education, 16, 440 (September) 1939.

Ambulatory Proctology

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INTRODUCTION

THE scope of ambulatory proctology has long been ill-defined. To most physicians the term connotes only the injection treatment of hemorrhoids. This is an unfortunate misconception. The field of ambulatory proctology is as broad as all proctology, for it includes both conservative and surgical techniques.

The physician who limits himself to injection therapy is an injection proctologist and not an ambulatory proctologist. This is an important distinction for the patient. If he is examined by an injection proctologist, too often the therapy advised is based upon the specialty of the physician and not upon the needs of the patient. Thus surgical hemorrhoids, fistulae, etc., may be treated by sclero-therapy rather than by surgery. There is no universal therapy for all proctologic pathology. Despite this obvious observation injection proctologists will treat all hemorrhoids, all fistulae,

7. The importance of careful, individual study of each patient is stressed so that the waters may be used with an intimate knowledge of the pathologic physiology, which is the basis for determining their definite indications.

pilonidal sinus and cyst, and pruritus ani by injections. There are indications for injection therapy, but they are limited.

Ambulatory proctology includes such surgical and medical therapy of proctologic pathology as may be performed in the office or in the hospital operating room with return of the patient to his home immediately after treatment. This includes the surgical and injection therapy of hemorrhoids, the surgery of most fistulae, the surgery of pilonidal sinus, cyst and abscess, the conservative and surgical therapy of pruritus ani, the surgery of cryptitis and papillitis, the surgery of anal, rectal and peri-rectal infections and abscesses, the surgery of benign growths of the anus, rectum and sigmoid, the surgery and conservative therapy of fissure in ano, the therapy and diagnostic study of proctitis and sigmoiditis, both specific and non-specific, the surgery and conservative therapy of anal stenosis and rectal stricture, the surgery of prolapse and most cases

of procidentia, and the fulguration therapy of malignancy in certain locations.

There are those who will take issue with me on the feasibility of operating hemorrhoids or extensive fistulae in the office and returning the patient to his home immediately after operation. Practical experience, however, has proven that very extensive surgery may

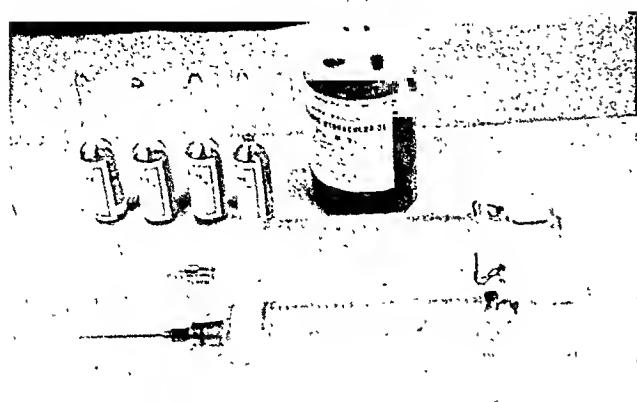


Figure 1
Analgesia Set: Syringe with large needle for injection of oil-soluble anesthetic (4 ampoules), and other syringe for injection of procaine solution.

be performed in a properly equipped office, under local analgesia, the patient being ambulatory immediately after operation.

I will here describe the general nature of such therapy, and the comparative value of hospital and ambulatory technique. The details of therapy have been described in other papers.

Hemorrhoids

Internal, uncomplicated hemorrhoids may be treated by injection therapy. Indeed, even prolapsing internal hemorrhoids may be treated by injection if the patient is informed of the limitations of such therapy. Physicians usually choose such therapy for themselves, even in the presence of prolapse, and with the full understanding that surgery is a preferable approach. They will rationalize that they are too busy to spare the time for surgery.

Injection therapy will cure internal hemorrhoids in all uncomplicated cases. It will temporarily cure prolapsing internal hemorrhoids, often for a period of years. It is of no value for external hemorrhoids, and should be employed with caution, if at all, in treating badly ulcerated hemorrhoids.

I prefer surgery for all complicated internal hemorrhoids. Surgery may be performed in the hospital under low spinal anesthesia if the patient prefers. If, however, economic factors militate against hospitalization, local analgesia in the office provides an equally satisfactory solution. The technique of operation is exactly the same whether performed in the office or in the hospital.

Proper local analgesia will permit adequate sphincter relaxation for complete exposure of the operative field. The only pain experienced is in the introduction of the

initial needles for infiltration. I employ initial procaine infiltration of the perianal skin and the sphincters, followed by infiltration with an oil-soluble anaesthetic solution. This provides for a comfortable post-operative course. Indeed pain is very rare following even the most extensive surgery. Post-operative oedema seems to be less frequent and less extensive in the ambulatory patient than in the bed-patient.

The operative technique may be clamp and ligature or clamp and cautery. I prefer the former. Partial excision, or ligature with subsequent sloughing are not recommended procedures. The surgical technique must be exactly the same whether the patient is operated in the office or in the hospital. It must be here emphasized that the only distinctions between office and hospital methods are in the analgesia and in the fact that the patient walks from the table and returns home to bed (or rest) rather than undergoing a stretcher trip to a hospital bed.

Cryptitis and Papillitis

Local analgesia is as above described with procaine and an oil-soluble anaesthetic, or the latter alone if preferred. Exposure of an isolated area is best obtained by the Smith retractor. Excision of the involved crypts or papillae is a rapid procedure. The patient may be returned to work the next day.

Fistula

The only permanent cure for fistula is surgical. Injection of sclerosing pastes and solutions may be successful in small tracts, but these are the types of fistulae most readily cured by surgery. Complicated extensive fistulae require careful, well-directed surgery.

Local analgesia with procaine will suffice for all but the most complicated of fistulae. As the tract is in-



Figure 2
Cantor Hemorrhoidal Injection Needles. The upper two needles are for the retrograde injection of hemorrhoids. The lower three needles are for superior pole or central point injection.

cised or excised the analgesia injection should lead the way, preceding the knife.

Whenever possible the exact extent of the tract should be determined by probing, or by injection of methylene blue in peroxide before surgery is performed. Roentgen localization with lipiodol or a comparable solution is rarely indicated.

I prefer incision to excision. It is simple and more rapid. Extensive scars and old abscess cavities must be excised, however, and excision may be carried up to the sphincter muscle. That part of the tract crossing the sphincter must be incised and not excised.

Certain rules are of value in determining the probable site of the internal opening.



Figure 3
This illustrates the use of adhesive strips to retract and expose the operative area. The patient is partially inverted on a Hanes table, preparatory to ambulatory hemorrhoidectomy. Pathology is acute ano-rectal prolapse with thrombosis of internal hemorrhoids.

1. If the external opening is within one inch of the verge the internal opening is usually at a point directly radial to this opening.

2. Most fistulae open into the posterior crypts.

3. If a fistulous tract extends from an anterior secondary opening, and crosses an imaginary transverse line bisecting the anus, the internal opening is usually at the posterior mid-line.

4. If the secondary opening is anterior to this line and over one inch from the anal verge, the tract will usually cross the line and open into a posterior crypt.

In most cases the ambulatory patient heals more rapidly than the bed-patient. No packing is allowed to remain between the cut sphincter ends more than twenty-four hours.

A word of caution should be added as to the mode of sphincter incision. It is best to cut the sphincter in only one place, and in a radial direction. I have established "points of election" for such incisions. These are at the anterior and posterior mid-line, and at the two directly lateral mid-points of the sphincter ellipse. In most cases, of course, the tract will open into posterior crypts and it will be a relatively simple matter to bring the line of sphincter incision to the posterior "point of election".

Fissure in Ano

Local analgesia and complete excision is the procedure of choice. In the early acute case underlying the ulcer area with a few drops of 5% quinine and urea hydrochloride may lead to eventual cure. Putting the sphincter at rest by injection of an oil-soluble anaesthetic will aid in hastening cure. Simple incision of the sphincter through the base of the ulcer may be required for cure, but excision of the entire ulcer together

with a contiguous area of skin is the best surgical procedure.

A chronic anal ulcer must always be excised. These patients may return to full activity the next day.

Pilonidal Sinus, Cyst and Abscess

Sclerosing therapy has little to offer in these conditions. In the occasional case such therapy will cure a readily accessible pilonidal cyst. The technique involves curettage of the tract and cyst as well as the injection of a sclerosing solution. But the treatment of choice, excision, involves such simple surgery that lesser and more fallible approaches seem illogical by comparison.

My own operation for pilonidal cyst is to outline the extent of the cyst by a mid-line and a bisecting transverse incision. When the borders are thus demonstrated an elliptical excision is performed connecting the outermost limitations of the initial crucial incisions. Thus the cyst is excised completely, and an extensive normal area need not be blindly removed with the pathology. Whenever possible the defect is immediately closed by deep retention and skin sutures. Do not bury catgut in the wound.

A pilonidal pressure pack over the dressings aids in obliterating deep dead space. This consists of an inflatable rubber bag incorporated in a broad belt, to produce pressure over the operative area.

Drainage through lateral counterincision is necessary if there is residual infection, evidence of sacro-coccygeal

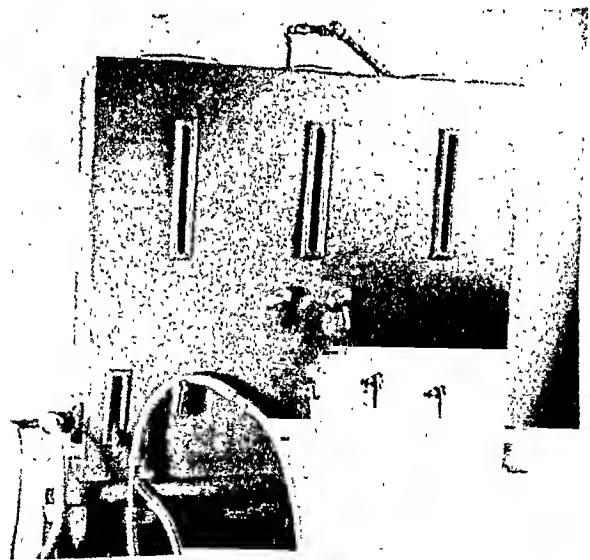


Figure 4
Original Colonic Irrigation Apparatus. Permits suction and pressure irrigation, in preparation for high sigmoidoscopy, and for the occasional case requiring therapeutic irrigation.

periostitis, or any question of complete obliteration of deep dead space and its concomitant accumulation of serum.

Ischio-Anal Abscess

Local analgesia is entirely satisfactory for the incision and drainage of peri-rectal abscesses, but caudal analgesia may be preferable. Ischio-anal abscess is

usually a complication of cryptitis, and incision will invariably be followed by a fistula extending from the involved crypt to the point of surgical drainage. For this reason the external incision should be placed as near as possible to the anal verge. It may be radial or parallel to the verge. Iodoform packing completes the procedure. The patient is instructed to take frequent

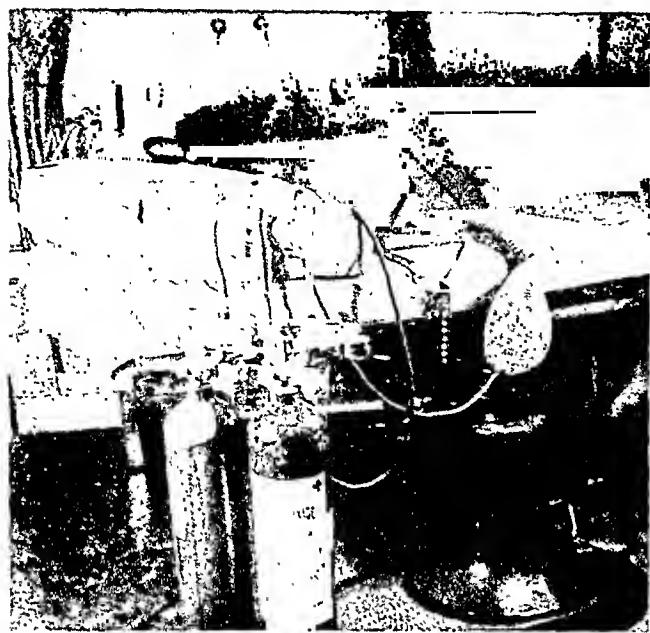


Figure 5
Nitrous-oxide-oxygen analgesia apparatus for bulb-administration, to ease discomfort of sigmoidoscopy in apprehensive patients. Hanes table and colonic apparatus in background.

hot sitz baths at home, and returns to the office for dressing the next day.

Anal Stenosis and Rectal Stricture

Dilatation is, of course, an office procedure. The surgery of anal stenosis is usually a posterior proctotomy followed by frequent dilatations, all readily ambulatory.

The therapy of rectal stricture will vary with the etiology, and the extent and nature of the stricture. Most strictures are sequelae of lymphogranuloma venereum infection. Diathermy, dilatation and other forms of conservative therapy are unsatisfactory. Internal or external proctotomy and various plastic procedures may be attempted. None are universally successful, and therapy must be carefully individualized. Complicated cases may occasionally require colostomy. This, of course, is not ambulatory.

Neoplasms

A polyp is often the forerunner of malignancy, and should always be removed. If sufficiently low in the rectum or anus, it may be excised easily after anaesthesia of the sphincters and retraction of the verge to expose the base of the growth. Excision must be complete and is preferred to coagulation. If the polyp is too high to be easily exposed for excision, fulguration through a suction equipped scope is satisfactory. A spark-gap machine gives the best fulguration spark and permits complete and rapid destruction of the polyp.

Always biopsy such a growth before fulguration.

Early malignancy, if below the peritoneal reflection and on the posterior rectal wall, may be treated by extensive fulguration. Complete excision of the rectum, however, is probably a preferable procedure.

Prolapse and Proctidinia

The treatment of a mild rectal prolapse or proctidinia may be either conservative or surgical. Sclerotherapy, employing a technique comparable to that described for the injection therapy of hemorrhoids, or by injection through long needles inserted just lateral to the verge and parallel to the lateral bowel walls, may be of value in early cases. Surgery offers a better prospect for permanence of cure.

Surgical techniques are also ambulatory. Local analgesia is adequate. Mild cases may be treated by excision of strips of mucosa and adjacent skin areas in several quadrants, comparable to the excision of hemorrhoids in a clamp and ligature operation. More advanced cases may require amputative techniques.

The most severe forms of proctidinia may demand an abdominal approach with obliteration of the cul de sac of Douglas, or a suspension procedure. These operations, of course, are not ambulatory.

Pruritus Ani

The treatment of pruritus ani may be conservative or surgical. In either event it is ambulatory. Conservative treatment is indicated in the early case with mild skin changes. In such cases analgesic ointments may be of value. An ointment containing cinnabar, Cinnacaine ointment, has proven very satisfactory. In every case the etiology must be determined and the cause treated.

In cryptogenic pernicious pruritus ani (i. e. undiagnosed chronic pruritus ani), my own procedure is to perform a tattoo-neurotomy. Mercuric sulphide (cinnabar) is tattooed into the perianal skin, followed by a subcutaneous neurotomy. Local analgesia is eminently satisfactory for this procedure, and the patient is immediately ambulatory. In one case the patient, (the male lead of a popular Broadway show), performed an active dancing and singing part the evening after the operation of tattoo-neurotomy!

CONCLUSIONS

Ambulatory proctology covers the entire diagnostic and therapeutic field of lower bowel pathology. It is not limited to injection techniques. The surgery of ambulatory proctology is exactly the same as that performed for the hospital patient. Local analgesia, employing an oil-soluble anaesthetic for its prolonged action, permits the patient to be ambulatory after operation in the proctologist's office.

The end-results are exactly the same as, and sometimes superior to, the hospital case. Post-operative oedema seems less prominent and less frequent in the ambulatory patient.

Whenever the economic consideration, or the preference of the patient, makes hospitalization undesirable, office ambulatory proctology is the perfect solution.

The Association of Squamous Cancer With Anal Manifestations of Lymphogranuloma Venereum

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SQUAMOUS carcinoma is the most frequent type of cancer originating in the anal canal. The incidence of anal cancer in patients with chronic anal manifestations of lymphogranuloma venereum suggests that the latter disease may be a predisposing factor in the genesis of this type of cancer.

The two diseases are usually encountered in patients who give a long history of rectal trouble. The average age of this group is lower than that of patients with squamous cancer of the anus who have negative Frei tests. The symptoms vary in accordance with the size and location of the cancer together with the extent of the non-cancerous lesion. Anal irritation is a common symptom, the severity varying from a mild annoyance to severe pain. Perianal itch, moisture of the perianal skin, anal incontinence, constipation, diarrhoea, bleeding, tenesmus, feeling of weight, etc., are not uncommon symptoms.

The clinical findings also vary widely. One of our patients had a small cancerous fissure in a sentinel pile, associated with a moderate inflammation of the anal canal but without any stricture or other manifestation of the venereal disease. The majority of patients have advanced non-cancerous anal disease, while the cancer may be large or small. Stricture formation, greatly thickened perianal skin, ulcers or fistulae and other advanced forms of anal and lower rectal lesions, may make the exact estimation of the cancerous process a difficult problem. The frequently enlarged inguinal nodes encountered in this group of patients may be neoplastic or inflammatory.

A review of the literature reveals a number of references emphasizing the relationship of these two diseases. David and Loring (1) report three cases of squamous carcinoma of the rectum which developed in long-standing lymphogranuloma venereum. Two of these had positive Frei tests but the third occurred before the present knowledge of the test, although there was good clinical evidence of the venereal disease. Cardwell and Pund (2) observed an additional case of epidermoid carcinoma of the anus which developed in the course of a long-standing lymphogranuloma venereum. The Frei test was positive. Lisa (3) reported an interesting case in which there was adenocarcinoma of the rectum and squamous carcinoma of the anus in a negro who had lymphogranuloma venereum with positive Frei and Wasserman tests. Pund, Greenblatt and Hine (4) in studying the microscopic findings in

various venereal diseases, stress the value of biopsy. In their series of cases of lymphogranuloma venereum they found three cases of carcinoma, one involving the anus, one of the labia and one of the penis. The importance of chronic antecedent lesions as causative factors in squamous cancer of the anus and rectum is brought out by Cattell and Williams (5) in a study of ten such cases.

It is of interest to note that in addition to the anal tumors, there are occasional reports of carcinoma of the vulva with lymphogranuloma venereum (2-4-5-9). This relationship has been mentioned by Taussig (6) in reviewing eleven cases of vestibular cancer. Nine had a history of syphilis and all had destructive granulomas or hypertrophic masses in the region of the vulva or rectum. The Frei test was positive in only three, but four cases were seen before the development of the test. In vulvar carcinoma the age of the patient is significant as regards the possible etiology. Smith (7) states that "the rare cases seen in women of the third decade are practically always superimposed upon skin lesions such as pruritis or lymphogranuloma venereum".

Squamous cancer of the anus is not a common disease, nor is it always associated with lymphogranuloma venereum. Many patients with this disease deny having any type of venereal infection and have negative Frei and Wasserman reactions. Patients in whom the two diseases are associated are usually from the lower strata of society, and include many colored. The white males infected usually belong to that class of males who are suspected of having abnormal sexual habits.

A review of the records of anal and rectal cancer at Memorial Hospital, New York, reveals 87 cases of the squamous variety. Nineteen of these patients were submitted to the Frei test. There were 8 positive and 11

Frei test in 19 patients with squamous cancer revealing 8 positive and 11 negative reactions.

Age	Males		Females	
	Positive	Negative	Positive	Negative
20-30	0	0	0	0
30-40	2 (white)	0	1 (colored)	1 (white)
40-50	2 (white)	0	2 (colored)	2
50-60	0	1	0	1
60-70	0	1	0	2
70-80	0	2	0	1

negative reactions. Of the remaining patients not submitted to the Frei test, there was clinical evidence

strongly suggesting pre-existing anal manifestations of lymphogranuloma venereum in many instances. The majority in the latter group were treated prior to the routine employment of this test.

The recognition of these two conditions in the same patient is important from the standpoint of treatment.

1. David and Loring: "Relation of lymphogranuloma to Development of Squamous Carcinoma of the Rectum", *American Surg.*, 109:837-843, May 1939.
2. Cardwell and Pund: *Journal of the Medical Association of Georgia*, 29:60-62, February 1940.
3. Lisa: "Adenocarcinoma of the Rectum, Squamous Cell Carcinoma of the Anal Canal and Chronic Tuberculous Pelvic Adenitis". *Arch. Path.* 21:252, February 1936, (New York Path. Society, November 26th, 1935).
4. Pund, Greenblatt and Hine: "Role of Biopsy in Diagnosis of Venereal Disease", *Amer. J. Syphilis, Gonorrhoea, and Venereal Disease*, 22:495-502, July 1938.

REFERENCES

5. Deibert and Greenblatt: "Malignancy and Lymphogranuloma", *Am. J. Syphilis, Gonorrhoea, and Venereal Disease*, 26:330-335, May 1942.
6. Taussig: "Prevention of Carcinoma of the Vulva", *Cancer Research*, 1:901-904, November 1941.
7. Smith, Frank R.: "Early Diagnosis of Malignant Tumors of Female Genital Tract", *Ill. Med. Journal*, 80:218-222, September 1941.
8. Cattell and Williams: "Epidermoid Carcinoma of the Anus and Rectum", *Arch. Surg.*, 46:336-349, March 1943.
9. Guzman, L.: "Coexistence of Chronic Lymphogranuloma and Cancer", *Radiology*, 41:151-156, August 1943.

A Clinical and Therapeutic Evaluation of Portal Cirrhosis^{††}

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Alcoholism Alone

OF THE several types of hepatic cirrhosis, by far the commonest is so-called portal cirrhosis. It is with the diagnostic and therapeutic aspects of this type that the authors are here particularly concerned. By portal cirrhosis we imply a progressive destructive process characterized by atrophy, fatty degeneration and necrosis of individual liver cells, with proliferation of new connective tissue and regeneration of new lobules. This results in parenchymal and vascular disorganization with subsequent portal hypertension. The distortion of the vascular and parenchymal structures in portal cirrhosis has been stressed by Moon (1), Mann (2), MacCallum and McNee (3), and others.

ETIOLOGY

While the potential etiological factors of portal cirrhosis are numerous, the cases we are primarily interested in are those with (1) alcoholism alone, (2) alcoholism with malnutrition, (3) malnutrition alone, and (4) a group of cases where no etiological factor for the cirrhotic process could be ascertained; this category we have designated as "idiopathic."

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Alcoholism and Malnutrition

Of the 104 patients with a definite history of alcoholism, 43 claimed a good diet, 33 admitted poor nutrition, and in 49, as previously stated, no clinical data was available either as to the dietetic regimen or alcoholism.

Malnutrition Alone, and "Idiopathic" Group

Seventeen patients gave a definite history of malnutrition, the diet being poor qualitatively and quantitatively. The most common explanation for the poor nutritional regimen given was poverty and absence of dentures. In 34 cases where exact clinical data was available, there was a history neither of alcoholism nor of malnutrition. These patients were placed in the "idiopathic" group for a lack of a known etiological factor. It is the purpose of this presentation to stress the symptomatology and therapeutic aspects of latent cirrhosis, since it is the early recognition and institution of proper treatment that offers the best prognosis. Latent cirrhosis may be symptomless; the factors initiating activity and decompensation are still not very clear. The frequency of an asymptomatic phase of partial cirrhosis is borne out by the numerous statistical reports on autopsies where patients who have died of other causes were also proven to have cirrhosis of the liver. At our own institution, 14 cases exhibited cirrhosis at necropsy with no clinical or laboratory evidence of its existence prior to death. Its significance is further proven by the fact that 64 of our 246 cirrhotics were admitted with no clinical evidence of liver involvement or, for that matter, no signs even suggestive of a cirrhotic process. In a series of 435 mentioned by Raimondi and Patek (8), cirrhosis was an incidental finding in 49. Rollerton and McNece (9) reported 52% latency in 160 cases seen at postmortem. McCartney (10) reported 35% latent cirrhosis in 245 autopsied cases. It is readily seen, therefore, that one-third to one-half of the cases may be asymptomatic. According to McCartney, a cirrhotic process can be arrested. In our own experience this is particularly true in the early cases, where no decompensation has taken place and where parenchymal involvement is minimal.

Early diagnosis of cirrhosis is difficult. This is understandable when one considers the complexity of the pathological process, with progression and regression of the disease depending upon relative rates of cell destruction and cell regeneration and upon the multiple physiological functions of the liver. All these factors produce marked variations in the clinical picture, and before decompensation takes place, systems other than the portal, either individually or in combination, may be implicated. In analyzing the clinical pictures of the early and late cases, one is impressed with the protein nature of the disease, particularly preceding decompensation. The diagnosis in all our cases was established by (1) clinical course and liver function tests, (2) peritoneoscopy, (3) laparotomy, and (4) necropsy.

SYMPTOMATOLOGY

Since cirrhosis may present such a variegated picture, we have attempted to emphasize the specific systems involved, with the predominating symptoms referable to that system. Where the collateral circulation is efficient and obstructive symptoms are in abeyance, the predominating symptomatology may be referred to (1) G. I. tract, (2) Hemopoietic system, (3) Peripheral and central nervous systems, and (4) Extra-hepatic

hiliary tract.

Gastro-intestinal System

In advanced cirrhosis, G. I. symptoms are commonly encountered. Dyspepsia, anorexia, loss of weight and change of bowel habit are the ones most frequently seen. In such late stages there are additional clinical and laboratory evidences either suggesting or supporting the presence of a cirrhotic process. In the latent phase, however, only a G. I. picture may be present. In 24 cases of our series where neither historical nor physical examination was suggestive of a hepatitis, the G. I. symptoms varied from a mild dyspepsia to a syndrome indistinguishable from that of malignancy. It is of interest to note that in 14 of these cases, where weight loss was not excessive, the duration of the symptoms extended from 2 to 10 years, emphasizing the potential latency of portal cirrhosis. "Morning sickness" was a common finding. This was stressed by Eppinger (11) who found it in 37% of 372 cases. Change of bowel habitus was frequent and consisted of alternating constipation and diarrhea, which when associated with weight loss and occult blood in the stools, was clinically indistinguishable from a large bowel malignancy. Often seen, too, was loss of weight varying from 5 to 20 pounds, not associated with other physical signs or symptoms. Anorexia alone was the only subjective complaint in 4 patients, anorexia associated with change of bowel habitus in 9 patients, anorexia with loss of weight was found in the rest of this group. Scandly (12) ascribes the anorexia to alcoholic gastritis, a finding confirmed by Askanazy (13), who noted evidence of alcoholic gastritis in 42 of 64 patients at autopsy. Five of our cases which were subjected to gastroscopic examination showed evidence of a chronic superficial gastritis. It must be stated that in all the above cases intrinsic pathology of the G. I. tract has been ruled out by (1) Roentgen examination, (2) Gastroscopy, (3) Clinical course and laboratory data. The exact diagnosis was confirmed by (1) exclusion of any other pathology, (2) repeated liver function tests showing deviations from normal, (3) peritoneoscopy, (4) gastroscopy, and (5) clinical course showing marked improvement with institution of proper therapy.

Hemopoietic System

The relationship between the hemopoietic system and the liver is clearly seen in chronic hepatitis. Any disturbance of the liver may express itself either in the form of anemia or in quantitative alterations of the components of the blood. The anemia may resemble the primary pernicious type, presenting differential difficulties even on sternal aspiration. The bone marrow may show a macrocytic hyperplasia, and improvement may follow liver therapy, with an increase in the reticulocyte count. Babonneix and Tixier (14) as early as 1913, reported a case of cirrhosis with a macrocytic anemia considered pernicious in type. According to Rossiter (15), the bone marrow of the middle third of the femur is typically red and hyperplastic, indicating an extension of normally active marrow.

Nine patients in our own series were admitted with

a tentative diagnosis of pernicious anemia. Hematological investigation, including sternal puncture, was highly suggestive of pernicious anemia. However, gastric analysis following histamine stimulation showed the presence of free acid, and further investigation confirmed the diagnosis of cirrhosis. It is of interest to note that the main symptomatology in this group consisted of dizziness, weakness, tingling and numbness of the lower extremities, and pseudo-tabetic gait. Physical examination was essentially negative except for evidence of severe anemia. The exact mechanism of this anemia is not clearly understood. It is possible that a diseased liver is incapable of either synthesizing or delivering the anti-anemic principal.

Where the secondary anemia dominates the picture, as it did in 87 of our cases, its cause may be either recurrent hemorrhage, or insufficient intake, absorption, and storage of iron. Twenty-three of these 87 patients were primarily admitted for subjective complaints of dizziness and weakness. There was no history of hematemesis or melena. Passive overdistension of esophageal varices may be responsible for concealed bleeding. According to Budd (16), the hemorrhage may at first be submucosal in nature, with oozing from unbroken surface of the mucous membrane. Unless repeated examination of the stools for occult or gross blood is frequently made, the bleeding may be entirely missed. In this group, bleeding peptic ulcer and ulcerating carcinoma were the most frequent tentative diagnoses made. It was only by a carefully elicited history of alcoholism, exclusion of intrinsic G. I. pathology, and repeated liver function tests that the diagnosis of cirrhosis was arrived at.

Another implication of the hemopoietic system in portal cirrhosis is the clinical manifestation of hemorrhagic tendencies. A hemorrhagic diathesis is frequently seen in chronic hepatitis as part and parcel of the disease, with other signs and symptoms indicative of portal cirrhosis. On the other hand, bleeding may be the only expression of a cirrhotic process. Fifty-five cases were associated with epistaxis, petechiae, purpura, or bleeding gums, with four of these being admitted primarily for purpura. Roch and Wohlers (17) noted 4.3% purpura, gingival hemorrhages or prolonged coagulation time in 431 cases of cirrhosis proved at autopsy. King (18) reported prolonged bleeding time in two of 13 patients, and abnormal clotting time in 11 of 36 patients. In none of our 4 cases, however, did we encounter any prolongation of the bleeding or clotting time.

Five cases were admitted primarily for recurrent epistaxis, with no other suggestive evidence, historically or clinically, of a cirrhotic process. Similar reports are not uncommon in the literature. It occurred in 33 of our 55 cases with hemorrhagic tendencies, and it was reported in 46% by Patek and Post (19). Nissen (20) noted epistaxis in 4 out of 77 patients.

The causes of the hemorrhagic diathesis include (1) low prothrombin, (2) thrombocytopenia, and (3) the presence of abnormal blood vessels (spiders) in the mucous membrane. The importance of thrombin in the

coagulation mechanism has been known for many years, and prothrombin, the precursor of thrombin, is a product of hepatic metabolism. Andrus and Lord (21) demonstrated the role of the liver in maintaining a proper prothrombin level in the plasma. Where parenchymal injury was minimal, restoration of normal prothrombin levels occurred when adequate amounts of vitamin K were available, whereas, on the other hand, when the damage was extensive, the level of the prothrombin could not be maintained or raised. In 30% of our pre-ascitic cases and in 65% of the total cases, the prothrombin level was low. In two of the cases of purpura and in three of epistaxis, the prothrombin level was below 35% of normal. It was significant that adequate administration of vitamin K failed to raise the prothrombin level in the ascitic cases if the ascites had existed for a period longer than eight months and if a long history of alcoholism was obtained. On the other hand, where ascites was either absent or of short duration, adequate administration of vitamin K usually restored the prothrombin level.

Snell, Vanzant and Judd (22) in 1930 were the first to report the occurrence of a severe thrombocytopenia in a case of long-standing hepatic disease and to suggest a relationship between the thrombocytopenia and hemorrhagic tendency. Morlock and Hall (23) have recently also emphasized that the prothrombin level is apparently not the only factor causing hemorrhagic tendencies in cirrhosis. Thrombocytopenia may be an additional cause. Morlock and Hall found it in 17.5% of 80 cases. According to them, the hemorrhagic tendency was evidenced in many of their cases, regardless of the blood platelets, but it was twice as frequent with associated thrombopenia. In a study of 100 cases of portal cirrhosis by King (24), a subnormal platelet count was found in 20%. In 25 of our cases with hemorrhagic tendencies, platelet counts were made (normals were considered between 150,000 and 250,000 per cu. mm.). In 18 cases, the count was normal, in 3 cases, it varied from 100,000 to 125,000 and in 2 cases between 70,000 and 90,000.

Vascular Spiders

The presence of vascular spiders in cirrhosis was recently reviewed by Patek, Post and Victor (25). According to Renou and Mignot (26) these spiders may appear long before clinical symptoms become apparent. Bloomfield (27) described a case in which the spider angioma disappeared with improvement of the symptoms. Of 75 cases of this series where spider angioma were looked for, they were found to be present in 37; usually they occurred in the face, upper trunk and occasionally on the arms and fingers. Cutaneous telangiectasia occurred in 7 of 75 cases. Their diagnostic importance was emphasized first by Eppinger and Cicovacki (28). Weber (29) and Cicovacki (30) suggested a common constitutional cause for the presence of these vascular lesions.

Hepato-biliary

Where the liver is the primary seat of the pathological process it is natural to expect that the hepatobiliary system should be clinically conspicuous by its

involvement. Where the liver and spleen were unequivocally palpable the possibility of a cirrhotic process was, naturally, immediately entertained. Seven cases, however, were admitted with symptomatology suggestive, rather, of being extra-hepatic in nature. In two of these, the symptoms consisted of severe colic, right upper quadrant pain, intermittent jaundice and fever. These symptoms were highly suggestive of a stone in the common duct. They were subjected to laparotomy and only cirrhosis was found. Three cases were originally admitted with pain and tenderness in the R. U. Q., and a history of intolerance to fatty food. A tentative diagnosis of cholecystitis was made. The remaining three cases of this group were admitted with a history of gradually increasing, painless jaundice with marked loss of weight, and the initial impression was that of a carcinoma of the head of the pancreas. The colic is explained on the basis of a sudden transitory toxic edema of the liver or a sudden hyperemia with distension of the liver capsule.

The palpability of the liver is not a very reliable sign. It varies in size in different cases and in the same case at different times. Marked diminution in the size of the liver may occur late in the disease and in most cases observed it is primarily enlarged. The hypertrophic stage is not always followed by atrophy, and in many cases the liver remains abnormally large throughout the course of the disease. This is true of those cases who die early in the disease or of intercurrent conditions. Palpability of the liver below the costal margin may be due to ptosis, fatty changes or mere hypertrophy without any pathologic changes. It was palpable in 60% of our cases while the spleen was palpable in 28% of the entire group.

Jaundice

Jaundice was present in 44% of our cases and it varied in intensity from a mild fleeting attack of a few days duration to one with a deep icterus lasting for weeks. Nine patients were admitted in a state of hepatic insufficiency characterized by confusion, disorientation, and deep coma from which the patient could not be roused. The jaundice was deep, the urine progressively diminished in output, with a rapid increase in the concentration of blood urea and a fall in the concentration of the cholesterol esters in the serum. The exact mechanism of jaundice in cirrhosis is not entirely clear. Ratnoff and Patek (31) analyzed autopsied protocols of 77 patients of cirrhosis with jaundice, and only half of this group had shown necrosis of the liver cells. It must be remembered, however, that absence of necrosis does rule out functional disturbances. In general, one can state that persistent jaundice in cases of cirrhosis denotes activity and implies a poor prognosis.

The neurological system is affected in portal cirrhosis both peripherally and centrally. The association of peripheral neuritis with cirrhosis has become more frequently recognized in recent years. Roger, Cornil and Paillas (32) reported 20 of 104 patients as having signs of alcoholic neuritis. Ratnoff and Patek found thirteen percent. In our own series careful neurological examinations were made in 137 patients. Twenty-seven per-

cent of this group showed evidences of peripheral neuropathy. This varied from an active neuritis to an old irreversible process indistinguishable from tabs. Cramps, muscular tenderness, and loss of Achilles and knee jerks were the most common findings. Where the central nervous system was involved, the illness was characterized by various degrees of emotional instability, varying from depression to euphoria, hallucination and paranoia. Five percent showed severe mental changes, and some of these patients had to be transferred to a psychiatric institution. Delirium and coma without icterus were observed in 3 cases. Thiersfelder (33) reported that these findings are common towards the end of the course of cirrhosis and emphasized that jaundice must not be present. Mental changes of a lesser degree were noticed in 9% of the entire series; these consisted of general dullness, forgetfulness, and diminished intellectual acumen. The neurological symptoms in portal cirrhosis have been claimed to be related to a co-existing nutritional deficiency. Snell (34) described encephalopathic states in diseases of the liver resembling the picture of acute alcoholism and acute pellagra. It is significant that some of the patients have responded promptly to large doses of nicotinic acid and thiamin. Patek and Post (35) reported mental changes in one-third of their series of cases and all, except those with myasthenia, improved with dietary therapy.

Decompensated Stage

Ninety-three cases were admitted in state of decompensation. The fully developed state of decompensation presents a fairly well defined clinical picture exhibiting some combination of abdominal distension, ascites, hepatic enlargement, splenomegaly and increased collateral circulation. There are, however, certain early obstructive phenomena which may be the first clinical evidence of a cirrhotic process and which may present diagnostic difficulties. Dependent edema was found in 11 cases with no apparent evidence of free abdominal fluid. In five of these cases ascites developed within five weeks of admission to the hospital. The dependent edema may be due to either an enlarged liver pressing upon the inferior vena-cava or to a hypo-proteinemia. Its significance lies in the fact that it may precede clinical ascites. Chronic bronchitis was found in nine cases. Its occurrence may be due to the fact that the veins of the bronchial mucosa discharge their blood posteriorly into the azygos veins, which communicate indirectly with the portal circulation.

Hematemesis

Vomiting of blood occurred in 63 of 246 cases. In 12 of these, it was the first sign indicating cirrhosis, and in 8 of these, the first hemorrhage proved fatal. In the non-fatal cases, the amount of the blood loss varied from a few ounces to a quart. In five cases the interval between bleeding episodes ranged from 8 to 12 years. In 17, the average interval was 20 months, with a fatal outcome after the third or fourth hemorrhage. Seven of those surviving the initial hemorrhage developed ascites within five days. It is generally stated that hematemesis follows rupture from esophageal varix. It is, however, frequently difficult to localize the point of

bleeding, and in five of our cases where the esophagus was carefully examined at autopsy, no bleeding points could be found, but the stomach showed marked hemorrhagic gastritis. Rolleston and McNee (36) believed that hematemesis may occasionally be due to a rupture of a gastric varix. Preble is of the opinion that hematemesis may occur in the absence of esophageal varices, and that the bleeding may be due to a rupture of gastrointestinal capillaries.

Ascites

One of the most outstanding obstructive signs in cirrhosis is, of course, ascites. It occurred in 93 cases of 246. Since the prognosis of the disease depends so much on the etiology of ascites, it is pertinent to review briefly the several causative factors of ascites. The foremost explanation for ascites is a mechanical one, namely a compression of the portal vein within the liver by contracting connective tissue. That this is not the only factor is proven by the fact that in many cases of definite cirrhosis, no ascites is found at necropsy. Hypoproteinemia frequently occurs in chronic diseases of the liver, and a disproportionate decrease in the serum albumen may reduce the colloid osmotic pressure and produce transudation. Hepatic injury as an additional factor in the causation of ascites, has been suggested by other observers, with an implication of a toxic injury to the capillary membranes. In attempting to determine the immediate factors responsible for the formation of ascites, it was found that the commonest causes were: (1) massive hemorrhage, (2) superimposed acute hepatitis, as judged by sudden onset of jaundice, marked abnormality of liver function tests, and a depletion of the plasma proteins to below the edema level.

Pleural effusion associated with ascites.

Vedel and Peuchi estimated the incidence of pleural effusions in cirrhosis as 1/6 to 1/7 in all cases and regard it as common manifestation of concomitant tuberculosis. In our own series we noted right-sided pleural effusions in seven cases, and left-sided in four. The effusions were non-hemorrhagic, and no evidence of tuberculosis was found. These effusions may be due to a number of factors: (1) a high diaphragm due to the ascites with subsequent stasis in the pulmonary vascular bed, (2) hypo-proteinemia with reduction of serum albumen, and (3) portopulmonary venous anastomosis.

Collateral Circulation

Among 93 decompensated cases with ascites, increased collateral circulation was noted in 67. Of 70 cases where ascites was absent, but the liver was palpable four to five fingers below the costal margin, 23 showed evidence of unusual collateral circulation. Jankelson and Baker (37) demonstrated by infra-red photography the presence of tortuous collateral veins in the abdominal wall before they were apparent to the naked eye.

Hemorrhoids

Rectal examinations for hemorrhoids were made in 87 patients, of whom 39 had ascites. Fifteen out of the 46 without ascites had hemorrhoids, while in the group with ascites, 21 patients had them. This would suggest

that the etiological factors for the hemorrhoids are portal stasis and pressure of the ascites upon the inferior vena-cava or hemorrhoidal veins.

LABORATORY DATA

As previously stated, the diagnosis of early cirrhosis presents great difficulties because of the highly variable clinical picture. In the absence of jaundice or hepatosplenomegaly, there is usually hesitancy in incriminating the liver, particularly when there is no clear-cut history of alcoholism or malnutrition. Recourse here to "liver function" tests may be of considerable aid in establishing or corroborating the diagnosis; often, too, these tests are of great prognostic value. The details of technic and interpretation of a simple "composite-test" we have used are reported elsewhere (38).

Of our 246 cases, 108 (44%) exhibited jaundice. The icteric index range was 8-20 in 56%, 21-40 in 18%, and 40-80 in 26%. The direct Van den Bergh reaction in these jaundiced cases was of the delayed type in 69%, biphasic in 22%, and immediate in 9%. This reaction was useful only in prognosis and in indicating the course of disease; it was unreliable for differential diagnosis.

The cephalin-cholesterol flocculation test proved excellent as an indicator of *active* hepatic pathology; a negative cephalin reaction did not rule out the presence of cirrhosis. This procedure was performed in 131 cirrhotics. The reaction was negative in 14% of 57 jaundiced cases, and in 58% of 74 non-jaundiced ones. In the jaundiced group, 72% exhibited 3+ and 4+ flocculations, while 14% had 1+ and 2+ responses. In the non-jaundiced group, only 19% showed 3+ and 4+ reactions.

Equally sensitive, and somewhat more reliable than the cephalin test, was the determination of the percentage of cholesterol esters. By our method, a figure below 65% is considered abnormal. According to this criterion, 55% of non-jaundiced cases gave abnormal results. In the jaundiced group the figures were even more impressive, with 86% of cases exhibiting an abnormal percentage of esters; of these, almost a fourth had ester values below 35% of the total cholesterol. The figures for total cholesterol were less revealing, the majority yielding values of 125-150 mg. per 100 cc. (normal range 150-200). Thirty-eight percent had elevated levels for total cholesterol (200-300), most of these occurring in either early alcoholic or moderately jaundiced cases. When the value for total cholesterol fell below 100 mg. per 100 cc., the prognosis was generally quite poor.

The alkaline serum phosphatase *per se* gave little help, but served very well as a corroborative test when used in conjunction with the other laboratory procedures. In the majority of cases, the values fell within the normal range, 2.0 to 5.0 Bodansky units. One-third had elevated levels, with occasional figures as high as 15-20 units; these occurred usually with jaundice, and were presumably due to either intrahepatic block or hepato-cellular irritation. In five cases with clinical and other laboratory evidence of severe hepatic damage, the

phosphatase values were below two Bodansky units.

Studies of the serum proteins, while not so valuable as classically asserted, nevertheless offered information of significant value, chiefly from the standpoint of prognosis. One-third of our cases exhibited normal values for total serum proteins (6.5 to 8.5 Gm. per 100 cc.). Sixty-two percent had subnormal levels, with 19% of these falling below 5.5 Gm. It is interesting that four percent of all cases were associated with high total protein values (above 8.5 Gm.); there was usually an accompanying hyperglobulinemia, and frequently, too, a mild jaundice. Subnormal serum albumin levels were present in 79%, with a low albumin : globulin ratio in 31% and a definite A:G reversal in another 42%.

The occurrence of ascites is directly related to the serum proteins. When the value for total proteins falls below 5 Gm., or that for albumin below 2.2 Gm., with a consequent A:G reversal, fluid almost invariably accumulates because of a decrease in intravascular osmotic tension. It is important to bear in mind, however, that ascites can occur in the face of normal protein values; this may be because of extreme portal hypertension, because of increased capillary permeability, or because of a qualitative change in the proteins. We have seen nine such cases. An even more unusual situation, which we have noted in seven instances, is the absence of ascites even though both total proteins and A:G ratio were abnormal; the explanation of this phenomenon may be simply that, although ascites was present, it was not susceptible to clinical detection.

TREATMENT

The therapeutic approach to cirrhosis has, in recent years, undergone radical changes. It is based upon the concept that nutritional errors predispose the liver to the action of toxins. This was substantiated by experimental work on animals and by clinical observations. It was found experimentally that when the liver was normal, it was difficult to induce necrosis of hepatic cells, while, on the other hand, necrosis could be induced if the chemical composition of the liver was made abnormal by dietary factors. It was also found that regeneration of the liver took place when a proper diet was supplied. With regeneration complete, it may functionally be normal and capable of maintaining the health of the animal in spite of gross cirrhotic changes. This view is also supported by clinical experiences. In a great percentage of patients admitted to a large charity institution such as the Metropolitan Hospital, where alcoholic histories could be elicited, there was also either a history of malnutrition or physical findings indicating poor nutrition. In a group of cirrhotics from whom a history of alcoholism could be obtained, malnutrition was the outstanding feature historically and on physical examination. It must be added, however, that there is quite a large group where historical evidences of neither alcoholism nor of dietary errors could be elicited. It is generally believed that the chemical integrity of the liver can be maintained by (1) high CHO intake, whereby a high hepatic content of glycogen is assured, (2) high protein both qualitative and

quantitative, (3) low fat, (4) proper intake of vitamin B complex. Thus hepatic injury by toxins may be prevented. With this as a background, 112 patients were treated and observed during a period of three and a half years. The results were compared with a group of 134 patients treated by (1) diuretics, (2) paracentesis and general supportive measures. Of the 134 cases treated with the latter regimen, 54 presented evidence of ascites. Of those that could be followed, 22 died within the first four months of admission, 12 died fourteen months later, and 10 were known to be alive twenty-three months later. Only 2 of the latter 10 have lost their ascites and the remaining 8 required frequent paracentesis. Fifty-three of the 80 non-ascitic subjects with enlarged liver, recurrent attacks of jaundice, and recurrent hemorrhages died in an average of 9.3 months. Seven appeared in good health three and a half years after the diagnosis of cirrhosis was made. Twenty patients could not be followed up.

In the group of 112 patients that were treated with a high protein, high CHO, low fats and multiple vitamin concentrates, 39 had ascites. Seven of the 39 could not be followed, and the clinical course of the remaining 32 was carefully observed. Fifteen of the 32 died within three months after admission, which is greater in percentage and shorter in duration than in the previous group treated with the old regimen. Six died within nine months and three within nineteen months. Eight lost their ascites, their nutritional status improved and at the time of this report seemed to be in good health. Of the non-ascitic group, 47 patients were observed during the period of three and a half years and 21 are, at present, in good health. Eleven died of hemorrhage, 5 of hepatic insufficiency, and 10 have had recurrent attacks of jaundice with general state of health not considered good. It would, therefore, seem that a high protein diet with the addition of vitamin concentrates influences, favorably, the course of the disease since 8 patients of 32 have lost their ascites and seemed to be in good health in comparison to 2 out of 44 with the old regimen. The rationale and the results of the highly nutritious regimen are more striking in the non-ascitic group where 21 of 47 are apparently in good health in comparison with 7 out of 60 with the old regimen. While the new therapeutic approach to cirrhosis offers a ray of hope, the mortality rate is still high with either regimen, particularly in the ascitic group. It is of interest to note that the best results were obtained in the following groups: (1) patients that were admitted with large livers which probably presented various degrees of fatty degeneration without extensive periportal fibrosis, (2) where multiple liver function tests showed minimal deviation from normal, and (3) where the clinical symptomatology was vague and physical findings equivocal, the so-called latent group. The conclusion that one can arrive at is that where extensive periportal fibrosis has taken place, the process is irreversible, and where the portal circulation is extensively impaired, the chances for regeneration of hepatic parenchyma are not good. Early diagnosis, recognition of the latent phase, and persistent treatment will probably offer better results.

SUMMARY

(1) A study of 246 cases of portal cirrhosis was made. (2) The recognition of the latent and early phase of the disease was stressed. (3) The early symptoms of cirrhosis are vague and may be exclusively referred to the G. I. tract, hemopoietic system, biliary tract, and to the nervous system. (4) A comparative evaluation

of the effects of a highly nutritious diet with vitamin concentrates in a group of 112 patients was made with the results in 134 treated by diuretics, paracentesis and general supportive treatment. (5) The best results were obtained in the non-ascitic group and in patients with the early phase of the disease where multiple liver function tests have shown minimal impairment.

REFERENCES

1. Moon, V. H.: Am. J. Med. Sci., 177, 681, 1929; Arch. Path., 13, 691, 1932.
2. Mann, F. C., and Bollman, J. L.: Arch. Path., 1, 681, 1926.
3. Mcnee, J. W.: Brit. Med. J., I, 1017, 1068, 1111, 1932.
4. Ratnoff, O. D., and Patek, A. J. Jr., Med. Vol. 21, 1942, p. 221.
5. Barker, L.: Intern. Clinics, 1, 17, 1929.
6. Bazzano, S.: Med. del Lavoro, 27, 303, 1936.
7. Eppinger, H.: Verhandl. d. Gesells. f. verhauungs. u. Stoffw., 5, 251, 1925.
8. Ratnoff, O. D., and Patek, A. J. Jr., Med. Vol. 21, 1942, p. 231.
9. Rolleston, H. D., and Mcnee, J. W.: Diseases of the Liver, Gallbladder, and Bile Ducts. Macmillan, London, 1929, 3rd ed.
10. McCartney, J. S.: Arch. Path., 16, 817, 1933.
11. Eppinger, H.: Verhandl. d. Gesells. f. verhauungs. u. Stoffw., 5, 251, 1925.
12. Saundby, R.: Practitioner, 74, 758, 1905.
13. Askanazy, M.: Schweiz. Med. Wochens., 12, 961, 1931.
14. Babonneix, L. and Tixier, L.: sur un cas de cirrhose compliquee d'anemie pernicieuse, Gaz. med. de Nantes, 1913, 61.
15. Rossier, J.: Etude sur l'etat de la moelle osseuse dans la cirrhose hepatique, Ann. d'anat. path., 1932, IX, 245.
16. Budd, G.: Diseases of the liver, Philadelphia, Blanchard & Lea, 1857.
17. Roch, M., and Wohlers, H.: Presse Med., 39, 1341, 1931.
18. King, R. B.: New Engl. J. Med., 200, 482, 1929.
19. Patek, A. J. Jr. and Post, J.: J. Clin. Invest., 20, 481, 1941.
20. Nissen, H. A.: Med. Clin. N. Amer., 4, 555, 1920.
21. Andrus, W. D., and Lord, J. W., Jr.: Arch. Surg. 41:596-606 (Sept.) 1940.
22. Snell, A. M.: Vanzant, F. R., and Judd, E. S.: M. Clin. North Amer. 13: 1417-1438 (May) 1930.
23. Morlock, C. G. and Hall, B. E.: Archives of Int. Med. July 1943, Vol. 72 No. 1.
24. King, R. B.: A Report Based on One Hundred Cases, New England J. Med. 200, 482, 484 (March 7) 1929.
25. Patek, A. J. Jr., Post, J., and Victor, J.: Am. J. Med. Sci. 200, 341, 1940.
26. Renon, L., and Mignot: Bull et mem. Soc. Med. d'hop de Paris, 3s, 39, 661, 1914.
27. Bloomfield, A.: Amer. J. Med. Sci., 195, 429, 1938.
28. Cicovacki, D.: Wien. klin. Wochschr., 53, 475-494, 1940.
29. Weber, F. P.: Brit. J. Wermat., 48, 182-193, 1936.
30. Cicovacki, D.: Wien. klin. Wochschr., 53, 476-494, 1940.
31. Ratnoff, O. D., and Patek, A. J. Jr., Med. Vol. 21, 1942, p. 244.
32. Roger, H., Cornil, L., and Paillas, J. L.: Nutrition, 7, 1, 1937.
33. Thiersfelder: V. Ziemssen's Cyclopedie of Med., 9, 1878 (Wm. Wood, N. Y.)
34. Snell, A. M.: Minn. Med., 23, 551, 1940.
35. Patek, A. J. Jr. and Post, J.: J. Clin. Invest., 20, 481, 1941.
36. Rolleston, H. D., and Mcnee, J. W.: Diseases of the Liver, Gallbladder, and Bile Ducts. Macmillan, London, 1929, 3rd ed.
37. Jankelson, I. R., and Baker, H.: Am. J. Dig. Dis., 5, 414, 1938.
38. Schwimmer, D., Klotz, S. D., Drektor, I. J., and McGavack, T. H.: A Fasting Blood Sample Procedure in the Differential Diagnosis and Management of Hepatic Disease. Am. J. Dig. Dis., 1, 1, 1945.

Gastritis Simulated by The Hyperfunctioning Stomach

By

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THE observations of Wolf and Wolff (1), as reported in their book, Human Gastric Function, will serve for many years as beacons for investigators in related endeavors. Possibly, gastroscopists will attempt similar studies of the intact stomach. One of the authors' most interesting contributions was their emphasis of the striking differences in appearance of the gastric mucosa brought about by the presence of food. This purely physiological engorgement caused by food always will remain unobserved at gastroscopy, for the stomach then is in a fasting and presumably resting state.

A major topic in their book is gastritis. The appearance of the hyperfunctioning stomach, whether

caused to overwork by "food, alcohol, histamine or certain emotionally charged situations," simulates that of "hypertrophic gastritis." This hypersecretiong stomach with its vividly described red, swollen succulent folds should not be confused with true hypertrophic gastritis. The essential features of the latter condition, as described by Benedict (2), Eusterman (3), Schindler (4) and others, are a velvety dullness and nodular segmentation of the folds which, although possibly enlarged, give the impression of rigidity. This rigidity of the folds in bona fide hypertrophic gastritis is quite the opposite of the boggy rugae noted in Tom's stomach. The histological picture in hypertrophic gastritis discloses a marked glandular proliferation and an abundant cellular infiltration of the entire mucosa, often with varying degrees of fibrosis of the submucosa. Just what a microscopic study of the mucosa of the

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hyperfunctioning stomach of man would show is not known, but the bulk of the swelling probably is a simple engorgement.

To make these distinctions certainly does not imply that the mucosa in Tom's stomach was at all times normal. In fact the authors' description of their subject's stomach after periods of sustained resentment tallies very well with what is termed superficial gastritis. This condition is associated with swollen reddened rugae, thick adherent mucus, and frequently with small erosions—precisely the picture seen through the fistulous opening. The histological appearance of the mucosa, under conditions of prolonged emotional unrest, of course will not be known without biopsy.

In this connection there is some rather convincing evidence presented by workers in the field of psychosomatic medicine which shows that certain types of

emotional instability may cause alterations in the mucosa of the intestinal tract. The classic investigations of White, Cobb and Jones (5) with patients having "mucous colitis" demonstrate this. Indeed, the possibility cannot be arbitrarily denied that in some instances long-standing anxiety might generate a gastritis. Proof of this obviously would be difficult, but some suggestion might be obtained by comparing the gastroscopic findings in normal individuals, as in Fitzgibbon's (6) group, with those of psychoneurotics.

It is hoped that Doctors Wolf and Wolff will continue their studies, and that gastroscopists will be stimulated thereby to aid in seeking a better understanding of the physiology of the stomach. By thorough acquaintance with the observations made by the two techniques both methods of investigation could, to a high degree, complement the other.

REFERENCES

1. Wolf, S. and Wolff, H. G.: *Human Gastric Function*, New York, Oxford University Press, 1943.
2. Benedict, E. B.: *Hypertrophic gastritis: Gastroscopic and clinical studies*, *Gastroenterology*, 1:62, 1943.
3. Eusterman, G. B.: *Chronic gastritis: Its place in modern medical practice*, *M. Clin. North America*, 23:847, 1939.
4. Schindler, R.: *Chronic gastritis*, *Bull. New York Acad. Med.*, 15:322, 1939.
5. White, B. V., Cobb, S. and Jones, C. M.: "Mucous Colitis—a Psychological and Medical Study of 60 Cases," Washington, D. C., National Research Council, 1939.
6. Fitzgibbon, J. H. and Long, G. B.: *A gastroscopic study of healthy individuals; a preliminary report*, *Gastroenterology*, 1:67, 1943.

Persistent Vomiting Due to Giardiasis

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FOR a long time the pathogenicity of *Giardia Lamblia* was in question. In the absence of an effective therapeutic agent, it was difficult to decide in any case whether the symptoms which were present were due to the Giardial infestation. Since the discovery by Galli-Valerio (1) that Atabrine was specific, making it possible to eliminate the *Lamblia* parasite completely in a short time, the consensus of opinion has been that *Giardia Lamblia* does cause gastro-intestinal symptoms, notably heartburn, belching and nausea.

The following case is reported because persistent vomiting without weight loss was the only symptom in an obese female, who had every outward appearance of a gastro-intestinal neurosis, and was so diagnosed for several years.

Case Report

D. G., a thirty-one year old married female was seen on November 10, 1942. She had given birth to a living child in November 1938. There had been persistent vomiting from the fourth to the eighth month of pregnancy. In May 1939, she again commenced to vomit. The vomiting was not associated with any nausea or pain and occurred after every meal. After two weeks it ceased spontaneously. She felt well until November

1939, when she began to experience severe headaches and occasional vomiting for several months. In June 1942, vomiting shortly after every meal recurred. There was no nausea or pain associated with the vomiting. There was occasional slight heartburn. The vomitus consisted of undigested food, always a fraction of what she had eaten and there was no loss of weight. There was no blood in the vomitus. There was never any diarrhea. The previous medical and surgical histories were negative. Catamenia was at thirteen years of age, every 25 days for three days.

She had consulted several physicians and gastroenterologists in reference to the cause of her vomiting and several roentgenographic studies of her gastrointestinal tract had been made. They revealed no abnormal findings, and her vomiting was considered to be on a psychoneurotic basis.

On examination, her weight was 131 pounds and height 61 inches. She was well nourished and did not appear acutely or chronically ill. The blood pressure was 128/80. The head and neck were negative. The heart and lungs revealed no abnormal findings. Abdominal examination was negative, with no tenderness or rigidity and no palpable masses or viscera. Pelvic and rectal examinations were negative. The extremities were normal and the reflexes were physiological.

Laboratory Data:—Hemoglobin 80%, Red Blood Count 4,440,000. White Count 8,750. Polymorpho-nuclear neutrophiles 60%, Eosinophiles 2%, Lymphocytes 36% and Monocytes 2%. Urinalysis was negative.

Cholecystography by the Graham-Cole method revealed a moderately large gall bladder which was well visualized, but which evacuated poorly after a fatty meal. There were no shadows of calculi.

Gastrointestinal X-rays revealed a normal esophagus, stomach and duodenum and a slightly spastic cecum.

Proctoscopy and barium enema revealed no abnormal findings.

Because of the failure of the gall bladder to evacuate sufficiently after the fatty meal it was decided to do a Lyons-Meltzer drainage. A, B and C specimens were

obtained. There was a normal color response. All of the specimens swarmed with motile Giardia Lamblia. The drainage was repeated one week later and the number of Giardia was considerably reduced but there were still many present.

On January 26, 1943, Atabrine 0.1 Gram was prescribed to be taken three times daily for five days. At the conclusion of this course there was a complete cessation of the vomiting. Gall bladder drainage done one week later showed many non-motile Giardia. Two weeks later no Giardia were found on biliary drainage.

The vomiting ceased on the third day after Atabrine was given, and there has been no recurrence to date. There have been no other gastrointestinal complaints.

It is reasonable to assume therefore, that the vomiting was due to the infection with Giardia Lamblia.

REFERENCES

1. Galli-Valerio, B.: La Lamblia et son traitement par l'atabrine. Schweiz Med. Wochenschr., 67:1181, Dec. 11, 1937.

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

CROWE, J. T.: Poisoning due to lye; value of Bokay prophylactic dilatation in prevention of early strictures of the esophagus. (*Am. J. Dis. Child.*, v. 68, p. 9, 1944.)

An analysis of 57 cases of lye swallowing revealed that the first aid given was generally poor because it was incomplete. Bokay prophylactic esophageal dilatation with a closed eyeless catheter containing metal shot or mercury can usually prevent secondary stenosis of the esophagus if carried out early. The longer the delay in treatment the more drastic must subsequent procedures be. Good results were obtained in 92 per cent of the patients because they received early attention.—D. A. Wocker.

STAMM, W. P., MACRAE, T. F., AND YUDKIN, S.: Incidence of bleeding gums among Royal Air Force personnel and the value of ascorbic acid in treatment. (*Brit. Med. J.*, v. 2, p. 239, Aug., 1944.)

The benefits to be derived from ascorbic acid in conditions of bleeding gums were investigated among Royal Air Force personnel. All subjects had been living on service rations for at least six months. Ascorbic acid tablets were given to alternate subjects, the others receiving dummy tablets of similar flavor. The ascorbic

acid dose was 200 mg. per day for one week and then 100 mg. per day for another two weeks. No great improvement was noticed. Both treated and control groups showed similar wide variations in the incidence and degree of bleeding.—F. E. St. George.

GOARDE, F. W., AND OLSEN, A. M.: Functional and organic disturbances of the upper part of the esophagus. (*Proceed. Staff Meet. Mayo Clinic*, v. 19, p. 482, Sept. 20, 1944.)

"Hysterical dysphagia is a well-defined clinical syndrome which affects elderly women with anemia and it is usually accompanied by loss of weight and nutritional deficiency." The patient may not be outwardly psychoneurotic. The condition is primarily hysterical in origin. The anemia is the result of inadequate iron intake. Chronic hypopharyngitis may perhaps interfere with normal sensations in the throat and so cause failure of passage of food through the lack of coordinated buccopharyngeal muscle activities. By the time a physician has seen the patient the normal physiologic mechanism of swallowing has been altered. Relief is prompt on passage of an esophagoscope, dilatation of a stenosis, and administration of iron and vitamins. Spasm of the cricopharyngeal muscle will cause dysphagia. The spasm may be the result of a lesion producing irritation of the hypopharynx. Therefore the diagnosis of "functional"

dysphagia should be arrived at only after careful examination. Carcinoma and other esophageal lesions may simulate functional dysphagia, especially if the patient happens to be neurotic. Mirror examination, roentgen examination and esophagoscopy should be made.—I. M. Theone.

STOMACH

MEYER, K. A., AND STEIGMANN, F.: *Surgical treatment of corrosive gastritis*. (*Surg. Gyn. Obstet.*, v. 79, p. 306, Sept., 1944.)

The sequelae of corrosive gastritis frequently do not appear until many months after the ingestion of the corrosive material. Consequently the sequelae, which may exhibit symptoms of pyloric obstruction, are often not associated with the taking of corrosive material. Case history should establish this point since there is no way of diagnosing corrosive gastritis before operation. Corrosive gastritis and carcinoma present similar features and the former may be mistaken for the latter. Corrosive gastritis should be recognized as such since this would permit pre-operative treatment aimed at building up the patient. Gastroenterostomy rather than resection may be done. The case histories of 4 patients with corrosive gastritis are presented.—F. X. Chockley.

BOWEL

SIBLEY, W. L.: *Meckel's diverticulum—dyspepsin Meckeli from heterotopic gastric mucosa*. (*Arch. Surg.*, v. 49, p. 156, Sept., 1944.)

Persistence of the vitellointestinal duct (or communication between the yolk sac and the midgut in the early fetus) is the deformity known as Meckel's diverticulum. Some type of Meckel's anomaly is present in about 4 per cent of all newborn infants. The diverticulum may occur at any point along the intestine and measure from a fraction of an inch to as long as two feet. Although the diverticulum may be present throughout life and cause no symptoms, it is always a potential source of pathology. About 15 to 20 per cent of all diverticula give rise to a pathologic condition.

The author reviews briefly but thoroughly the pathology and clinical aspects of the condition. Fifteen drawings in three sets of figures illustrate very clearly the formation of the diverticulum and the various anatomic types that may be found.

The diverticula are classified according to the scheme of Greenblatt and coworkers, namely as the ulcer type, obstructive type, diverticular type, umbilical type, tumor type and incidental type. Each type is further subdivided into groups according to either the pathological process or the anatomic area involved. Symptoms and treatment are described and twelve case histories are presented. Treatment is surgical and should be carried out as soon as a diverticulum is suspected. In some cases a symptom complex is found due to heterotopic gastric mucosa in the diverticulum. This is probably due to the action of pepsin and hydrochloric acid secreted by this mucosa. The term dyspepsia Meckeli is suggested.—G. A. H. Tice.

THOMPSON, G. F., AND FOX, P. F.: *Perforated solitary diverticulum of the transverse colon*. (*Am. J. Surg.*, v. 66, p. 280, Nov., 1944.)

Diverticulitis of the transverse colon is rare. Sixty to eighty-five per cent of diverticula of the colon are in the descending colon and sigmoid. The least frequent though most serious complication of diverticulitis is sudden perforation into the peritoneal cavity with resulting peritonitis. Most acute perforations have been reported as occurring in the sigmoid or descending colon. Diverticulitis usually signifies the presence of multiple diverticula.

The case is reported of a 35 year old male who had an acute perforating diverticulitis of the transverse colon. Excision of the involved diverticulum together with the adjacent colon segment was performed. The colostomy was later closed. Barium enema revealed no other diverticula.—D. A. Wocker.

KLEIN, A., AND PORTER, W. B.: *Intestinal malabsorption associated with mesenteric lymph node tuberculosis*. (*Arch. Internal Med.*, v. 74, p. 120, 1944.)

The patient was a 16 year old boy with diarrhea, tetany and edema. Studies were carried out for a period of four years and showed his glucose tolerance curve to be flat, BMR decreased, hypocalcemia and hypoproteinemia. Amino acid administration was found the only effective method of bringing his serum protein levels up to normal. Chronic tuberculosis of the mesenteric nodes was found at autopsy. It was considered that the impaired intestinal absorption due to the tuberculosis was responsible for the symptoms—G. Klenner.

PANCREAS

COMFORT, M. W., BUTT, H. R., BAGGENSTOSS, A. H., OSTERBERG, A. E., AND PRIESTLEY, J. T.: *Acinar cell carcinoma of pancreas: Report of case in which function of carcinomatous cells was suspected*. (*Ann. Internal Med.*, v. 19, p. 808, 1943.)

In a case of acinar cell carcinoma of the pancreas, the values for lipolytic activity and particularly for amylolytic activity in the serum and the ascitic fluid were exceedingly high. It is possible that the high values were due entirely to obstruction of the pancreatic ducts, to obstructive pancreatitis or to absorption of enzymes from the pancreas and a pseudocyst. The values for enzymes were so much higher, however, than in any other case of carcinoma of the pancreas that some other explanation was sought. The possibility that the high values were due to functioning of the acinar cell carcinoma was examined and, while the data have been too incomplete to warrant the conclusion that the carcinoma was functioning, the possibility is an attractive one that deserves consideration in future cases of carcinoma of the pancreas with high values for amylolytic and lipolytic activity in the serum. The case has been reported to call attention to the possibility that acinar cell carcinomas of the pancreas may function and may be responsible for high values for enzymatic activity in the serum.—Biological Abstracts.

LIVER AND GALLBLADDER

STACEY, R. S.: *Portal cirrhosis in Iraq.* (*Trans. Roy. Soc. Trop. Med. and Hyg.*, v. 37, p. 387, 1944.)

Portal cirrhosis in Iraq is described on the basis of a study of 136 cases. Comparisons are made with the disease as known in Europe and America. The value of the use of the "formol reaction" and of the "serum euglobulin estimation" in differential diagnosis is indicated. The disease in Iraq is associated with poverty and the resultant food deficiency, particularly of animal proteins. Such deficiency makes the liver hypersensitive to toxins that normally would have little effect. No alcoholism exists in Iraq among the natives and therefore plays no part in causing cirrhosis. This is quite different from the picture in the Occident.—Courtesy Biological Abstracts.

FAUST, D. B., AND MUNGETT, C. S.: *Visualization of the biliary tract with air and barium following a barium meal.* (*Am. Internal Med.*, v. 19, p. 356, 1943.)

In discussing the mechanism by which air and barium, following a barium meal, appear in the gall bladder or bile ducts, or both, a comprehensive review of the literature on the subject was presented. In cases previously reported the appearance of air in the gall bladder was due either to a gas bacillus infection of the gall bladder, or to a fistulous communication from the biliary tract to the stomach, the duodenum, or the colon, either spontaneous or surgical in origin. Numerous instances were found in the literature in which the biliary tract in part or as a whole was outlined with barium following a barium meal or a barium enema, but without air being noted in the biliary tract. In these cases spontaneous or surgical biliary fistulae were present in the great majority. Seventeen cases had been reported in which no fistulae were demonstrated but the biliary tract was outlined with barium to a greater or lesser extent. In none of these cases was air noted in the gall bladder or the bile ducts. After a review of these cases the expressed opinion was that the accountable mechanism was an incompetent sphincter of Oddi which permitted the entrance of barium into the biliary tract. The conditions most frequently associated with incompetency of the sphincter of Oddi were duodenal ulcer and tumors of the upper abdomen. The symptoms varied but in most instances were referred to the upper abdomen. The case reported was unusual in that nowhere in the literature was a case found in which the biliary tract was visualized with air in the gall bladder and no fistula present. Films of the gastro-intestinal series are shown. Laparotomy disclosed cholecystoduodenal adhesions. The release of the adhesions and dietary measures resulted in symptomatic relief.—Biological Abstracts.

ULCER

BLUM, S. D.: *Peptic ulcer of greater curvature of stomach.* (*Am. J. Roentgen. Rad. Therap.*, v. 52, p. 291, Sept., 1944.)

Benign ulcer of the greater curvature of the stomach is so rare that only 15 proved cases have been reported

in the literature. When roentgenologic examination shows a niche on the greater curvature, this should be taken as evidence of a malignant lesion until further examination proves it benign. The author gives the case history of a patient with proved ulcer of the greater curvature who showed no signs of ulcer six months after operation.—F. X. Chockley.

THERAPEUTICS

CRAWFORD, B. G. R.: *Post-anæsthetic vomiting.* (*Brit. Med. Jour.*, v. 1944, p. 826, 1944.)

Oral administration of 5 to 20 minims of 1 in 1000 adrenaline chloride in an ounce or so of water, repeated with safety if necessary, will control vomiting in most cases.—Biological Abstracts.

STAVOSTENKO, N. T.: *Requirements of vitamin C in chronic gastritis, cholecystitis and in colitis.* (*Soviet Med.*, (No. 15), p. 27, 1940.)

Hypovitaminosis C is shown by most patients suffering from cholecystitis, colitis and chronic gastritis. Addition of 60 to 80 mg ascorbic acid to the diet has brought promising results in a number of patients with these diseases.—G. Klenner.

SURGERY

BURGHARDT, M.: *Gallbladder surgery.* (*Am. J. Surg.*, v. 65, p. 203, Nov., 1944.)

This paper reviews 212 operations for gallbladder disease performed during the five year period 1939-1943 inclusive. Four times as many women had gallbladders removed as men while three times as many women had gallstones as men. Most patients with gallstones were between 35 and 55 years old, the range in ages for this series of patients being 15 to 74 years. In 4 of 166 gallbladders removed there was no pathology and one contained stones. The remainder showed varying degrees of pathology, three of which extended to the point of perforation. Except for a small number, all patients had pain. Nausea, vomiting, and gas belching were outstanding symptoms. Bloating, heart burn and sour eructations were other symptoms. Patients with primary acute cholecystitis were often operated as soon as admitted to hospital. The upper right rectus incision was commonest. Spinal anesthesia was the anesthetic of choice. Cholecystectomies were usually drained. The most frequent complications were atelectasis, pneumonia and cardiac disease. Mortality was six per cent, pneumonia and cardiac failures accounting for the largest number. The routine administration of carbogen at repeated intervals after surgery, deep breathing and frequent changes in position, administration of fluids to overcome dehydration, blood transfusions, vitamin K injections and the sulfa drugs are listed as the main procedures and drugs for both prophylactic and therapeutic use.—F. X. Chockley.

KISNER, W. H., AND ALDEN, R. L.: *Penetrating wound of the abdomen treated with penicillin.* (*Am. J. Surg.*, v. 66, p. 259, Nov., 1944.)

This is a case report to illustrate the severe type of penetrating wound of the abdomen that is very fre-

quently seen in modern warfare. A 31 year old soldier received a hand grenade wound in the lower right quadrant. Within about 30 minutes he was admitted to the operating room in condition of shock. The wound was extensive. The abdomen was sponged clean of blood and feces but was not lavaged. Bleeding points were tied and the portions of the small and large intestine which were lacerated were resected. The retroperitoneal tear was sutured. Ten grams of crystallin sulfanilamide were sprinkled in the body cavity. Plasma and blood transfusions were given and intestinal decompression by an indwelling tube was done.

The patient's condition was worse on the second post-operative day and 30,000 Oxford units of penicillin every 3 hours were given. Sulfonamides were discontinued. On the tenth day penicillin was no longer required, since the patient was greatly improved.

The authors believe that in penetrating wounds of the abdomen penicillin may prove to be the chemotherapeutic agent of choice when surgical procedures and blood transfusions have been carried out to correct the lesions and to combat shock.—F. X. Chockley.

SLOAN, H. E., JR.: Perforating abdominal injuries with special reference to reduction in mortality by use of transfusions and sulfonamides. (*Surg. Gyn. Obstet.*, v. 79, p. 337, Oct. 1944.)

Between 1925 and 1943 there were 146 cases of perforating abdominal injuries subjected to exploratory operations at Johns Hopkins Hospital. These included 55 puncture wounds and 91 gunshot wounds. The mortality rate was 31 per cent from 1925 to 1938 and 10 per cent from 1939 to 1943 although the same operative technic was used. The reduction in mortality rate was directly attributable to the use of sulfa drugs and use of transfusions. Improved anesthesia provided only a small percentage of this reduced mortality rate. Transfusions combatted shock which made the patient susceptible to infection. Hence transfusions probably had a greater influence than the sulfonamides. While the marked successes obtained in a large hospital cannot be reproduced in the battle field, the use of sulfa drugs and transfusions can nevertheless reduce greatly the mortality from traumatic perforating wounds of the abdomen.—F. X. Chockley.

EXPERIMENTAL MEDICINE

MOTILITY

VAN LIERE, E. J., NORTHRUP, D. W., AND STICKNEY, J. C.: The effect of anemic anoxia on the motility of the small and large intestine. (*Am. J. Physiol.*, v. 142, p. 260, Sept., 1944.)

Matched pairs of animals previously fasted 24 hours were used, one animal serving as a control and the other as the experimental. A test meal of 50 cc. suspension of 10 per cent powdered charcoal in 10 per cent aqueous gum acacia was administered by stomach tube to each animal. Only the experimental series were subsequently subjected to hemorrhage.

While in the control group the test meal traversed

55 per cent of the length of the small intestine, in the group subjected to hemorrhage (equivalent in degree to 3 per cent of body weight) the intestinal length traversed during the same period was 74 per cent. This accelerated intestinal motility is interpreted as being due to parasympathetic stimulation by the anemia anoxia.

As recorded by the enterograph, the longitudinal muscles of the colon showed lowered tone and/or frequency of contraction. A few of the animals were found highly resistant to the anemic anoxia.—I. M. Theone.

BADKIN, B. P., AND BORNSTEIN, M. B.: The effect of swinging and of binaural galvanic stimulation on the motility of the stomach in dogs. (*Rev. Canad. Biol.*, v. 2, p. 336, Aug., 1943.)

Certain dogs are susceptible to swinging movements and develop motion sickness. In these susceptible dogs swinging inhibited immediately all gastric motor activities and in 5 to 15 minutes induced vomiting. In a few animals gastric tone and hunger contractions returned gradually to normal patterns after cessation of swinging. However, more often there would appear a special rhythmic vestibular type of gastric contractions. Commencing in 15 minutes to 2 hours, these contractions were not affected by atropine nor induced by prostigmine. In two susceptible dogs motion sickness was abolished by bilateral labyrinthectomy. The conclusion was drawn that the gastric phenomena associated with motion sickness were due to excessive vestibular stimulation.—M. H. F. Friedman.

ABSORPTION

FAVARGER, P.: Cholesterol and fat absorption. (*Arch. internat. pharmaco.*, v. 68, p. 409, 1942.)

Elaidic acid esterifies with cholesterol in the intestine. This is taken as evidence in support of the view that some of the fatty acids are absorbed from the intestine in the form of their cholesterol esters.—G. N. Smith.

PATHOLOGY

WAKIM, K. G.: Effect of certain substances on the intrahepatic circulation of blood in the intact animal. (*Amer. Heart J.*, v. 27, p. 289, 1944.)

The circulation of blood within the vascular system of the liver was studied in intact animals by means of the quartz-rod illumination technique. Intrahepatic circulation was found to be increased by administration of glucose. India ink and other particulate matter as well as dyes also increased intrahepatic circulatory activity. The India ink loaded the Kupffer cells shortly after injection because of the phagocytic activity of the cells. Sinusoids showed varying degrees of vascular potency. Thyroxine caused increased vascularization to the extent that few sinusoids were left inactive; on the other hand adrenaline effected constriction of the intrahepatic vascular system to the extent that the liver was noticeably blanched. Acetylcholine had no vasodilator effect on the liver blood vessels.—G. N. N. Smith.

NASIO, JUAN: *Urogastrone in the treatment of gastro-duodenal ulcer.* (*Anales Dispens. Pub. Nac. Enferm. Afavor. Digest.*, v. 6, p. 155, 1943.)

Urogastrone is a substance excreted in urine which has been found to inhibit gastric secretion and motility and to prevent formation of experimental peptic ulcers. The literature on urogastrone is reviewed and the physical, chemical, and biological properties are presented in tabular form. Depending on the source of urine from which the urogastrone is prepared, the inhibitory effects on the stomach vary greatly. The amounts excreted also vary. Due to difficulties in preparing urogastrone the results of clinical trials are uncertain. From the published report Nasio concludes that urogastrone has a definite therapeutic value. He points out that the pathogenesis of peptic ulcer may be explained by the absence of urogastrone from the individual.—D. J. Abolosia.

ZINTEL, H. A., RIEGEL, C., PETERS, R., RHOADS, J. E. AND RAVIN, I. S.: *Intravenous administration of dextrose in the treatment of patients with disease of the biliary tract.* (*Arch. Surg.*, v. 49, p. 238, Oct., 1944.)

A group of 50 patients with diseases of the liver had biopsy specimens of the liver taken. Before operation 18 of these patients received dextrose intravenously while the remaining 40 patients served as controls and received no preoperative dextrose mediation. The patients receiving dextrose showed 118 per cent more liver glycogen than the controls. Intravenous administration of dextrose without dietary supplement did not lower the liver content in the patients observed.—M. H. F. Friedman.

DAVIS, J. E.: *Experimental production of a hyperchromic anemia in dogs which is responsive to anti-pernicious anemia treatment.* (*Am. J. Physiol.*, v. 142, p. 402, Oct., 1944.)

Daily administration of choline chloride to normal dogs produces significant lowering of the erythrocyte count within 10 to 15 days. The anemias produced are hyperchromic and probably due to a decreased rate of erythropoiesis. When adequate doses of purified liver extract are administered intramuscularly, the erythrocyte count returns to normal in 1 to 4 weeks. This erythrocytic response to liver extract occurs even though choline is still being administered. A similar return to normal red cell count was obtained after twelve days of feeding stomach U. S. P. Atropine sulfate given orally 3 times daily to one anemic dog caused his red cell count to return to normal in 4 weeks although the choline feedings were still being continued.—M. H. F. Friedman.

SINGHER, H. O., KENSLER, C. J., TAYLOR, H. C. JR., RHOADS, C. P. AND UNNA, K.: *The effect of vitamin deficiency on estradiol inactivation by liver.* (*J. Biol. Chem.*, v. 154, p. 79, 1944.)

Employing liver slices from animals grown on both normal and deficient diets it has been possible to show

that the inactivation of estradiol is dependent upon the tissue riboflavin and thiamine content. When liver riboflavin values fall below 13-14 gamma per gram of liver, systems essential for the estrogen inactivation no longer function as in the normals. The inactivating ability can be restored by feeding riboflavin. The reappearance of estradiol inactivation follows the use of liver riboflavin. A similar course of events occurs with thiamine depletion. Pyridoxine, pantothenic acid, biotin and vitamin A deficiencies are without effect upon the ability of the liver to inactivate estradiol.—Courtesy Biological Abstracts.

PATHOLOGICAL CHEMISTRY

BOYD, E. M.: *Species variation in normal blood lipids estimated by oxidative micromethods.* (*Canad. J. Research, (Sect. E, Med. Sci.)*, v. 22, p. 39, Apr., 1944.)

The values reported in the literature for blood lipids are often contradictory and confusing because of the variety of methods used in the determinations. The present comparative study used the same methods of analysis throughout. Blood plasma lipids of the bullfrog were found to be low, as also were those of the guinea-pig. Bullfrog plasma showed no neutral fat but instead showed a rather high content of cholesterol esters. The lipid content of the blood plasma in the dog was found higher than in man while the reverse was found for the cholesterol esters. While the lipid content of the plasma showed species differences, the lipid content of the red blood cells was found to be the same in all the species studied. This emphasizes the point that plasma or serum rather than whole blood should be selected for study when blood lipid determinations are required since red cell lipids are constant in spite of wide variations in plasma lipid concentration.—Horace Stilyning.

METABOLISM AND NUTRITION

CAVINESS, V. S.: *Carotenemia.* (*North Carolina Med. J.*, v. 5, p. 432, Sept., 1944.)

Carotenemia is probably more common than is shown by the reports in the literature. It is most frequently confused with, and reported as, biliary jaundice. To distinguish between the two, the following points are emphasized about carotenemia: 1. The urine is negative for bile, 2. the urine is usually less intensely colored, 3. there is no itching of the skin, 4. there is no yellowing of the scleras, 5. yellowing of the skin is most prominent in the palms, soles and nasolabial fold, 6. blood bilirubin is within normal range, 7. blood carotene is high, 8. the stool color is normal. Because of the high role carotene-containing foods play in their diet (mainly vegetables), carotenemia is usually seen in children and diabetics. The present paper reports carotenemia in two adult diabetics.—D. A. Wocker.

BOYD, J. *The need for betterment of children's diets.* (*J. Am. Dietetic Assoc.*, v. 20, p. 147, 1944.)

Cumulative experience of the past 18 years with groups of children regimented so as to ingest optimum diets has shown these children to stand out in sharp

contrast with children whose diets have been unsupervised. Dental records have offered the most tangible evidence in favor of dietary supervision. The great prevalence of dental caries is assumed to be one of the best proofs that the average child's dietary is not adequate. Tooth decay is not the only handicap imposed by faulty diet. Betterment of dietary habits of children is a matter of education, both of children and of responsible adults.—Biological Abstracts.

JOSEPHS, H. W.: *Hypervitaminosis A and caroteneemia*. (*Am. J. Dis. Child.*, v. 67, p. 33, 1944.)

A male child three years old had received 240,000 units of vitamin A each day since he was 3 months old. Hepatomegaly, splenomegaly, leukopenia, hypoplastic anemia, clubbing of fingers, coarsening of hair and precocious skeletal development resulted. This picture of severe hypervitaminosis A cleared when the excess vitamin A was withheld from the diet.

A mechanism probably exists which controls blood levels of vitamin A but not for carotene. This mechanism may perhaps be related to reticulo-endothelial functions. In the case presented either the regulatory mechanism was damaged by excessive intake of the vitamin A or else it was defective for other reasons and failed to regulate vitamin A blood levels.—D. A. Wacker.

MISCELLANEOUS

LOLLI, G., RUBIN, M. AND GREENBURG, L. A.: *The effect of ethyl alcohol on the volume of extracellular water*. (*Quart. J. Stud. Alcohol*, v. 5, p. 1, 1944.)

Fed as well as fasted rats received ethyl alcohol solutions by either stomach tube or by vein. Extracellular fluid volumes were determined at intervals of 2, 4, 6, or 20 hours. The extracellular fluid was measured on samples of blood taken from the heart. In all cases, either intravenous or intragastric administration of alcohol resulted in an increase of extracellular fluid

which represented an actual loss of intracellular fluid.
—G. N. N. Smith.

COUTINHO, A. AND DE MELO, A. C.: *Some comments on the Exton-Rose glucose tolerance test*. (*Hospital (Rio de Janeiro)*, v. 25, p. 295, 1944.)

Interpretation of results of the Exton-Rose test is discussed, with presentation of data in 21 tests. The importance of liver function and gastroenteric motility in determining the results is noted.—Courtesy Biological Abstracts.

KATLYAROV, I. I.: *Liver amylase during pregnancy*. (*Bull. Biol. Med., U. S. S. R.*, v. 11, p. 70, 1941.)

The activity of liver amylase is decreased during pregnancy. Adrenaline does not affect the liver amylase activity in vitro.

MAYER, H., JR. *Passage of Miller-Abbott tube thru pylorus with aid of electro-magnet*. (*U. S. Naval Med. Bull.*, v. 43, p. 463, Sept., 1944.)

To overcome the difficulty of getting the tip of the Miller-Abbott tube to pass thru the pylorus, the tip is constructed from a non-corrosive, highly magnetic alloy, alnico. The Miller-Abbott tube is passed into the stomach in the usual manner. When the end of the tube is seen by fluoroscope to lie against the pyloric sphincter, the patient is turned in the right anterior oblique position. While the tube tip is under fluoroscopic visualization, an electromagnet is applied against the right flank and advanced in the same direction as the duodenum. When the tube is allowed to slowly pass down from above, the tip will be seen to pass readily into the duodenum. Once the tip is past the duodenum the electromagnetic is no longer required, and the remainder of the procedure is carried thru in the usual manner. The author claims that the tube can be passed thru the pylorus in about one or two minutes and that in his hands it has always been successful.—Horace Stilyung.

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Orientation of the Gastroscope By Roentgenograms

By

A. RAY HUFFORD, M.D.

and

G. G. STONEHOUSE, M.D.

GRAND RAPIDS, MICHIGAN

INTRODUCTION

RADIOGRAPHY was utilized in this particular study during gastroscopy, in order to facilitate a better understanding of what actually happens to the gastroscope, and to the anatomical structures through which it passes, during a routine gastroscopic examination.

The gastroscope as an aid in diagnosis is becoming more evident each year, and is coming into a special field of its own which it rightfully deserves. It is quite evident that more knowledge of the gastroscopic action must be obtained in order to make the proper progress in this newer field of diagnosis. In order to observe what occurs to the anatomical structures and to the flexible gastroscope *in situ*, as well as to gain a better understanding of the so-called blind spots, and their locations, seems best obtained by this type of study.

Of great interest and certainly of great concern to the gastroscopist is the question of stress or strain to the anatomical structures which lie adjacent to the scope.

During the gastroscopic examination only a part of the stomach is in view at any one time. As the gastroscopist is unable to visualize any part of his scope during such an examination and its relation to the stomach as a whole, he is only able to orient himself by his knowledge of the landmarks in the stomach. What is actually occurring to the scope during its passage and while viewing the various parts of the stomach is unseen and unknown to him, except as the examiner judges relative distances and positions by the feel of the scope, and the appearance of the area which is being examined.

MATERIALS AND METHODS

Two patients were chosen for this study. Both had negative x-rays of the esophagus, stomach and duodenum, and both were gastroscopically negative.

The pregastroscopic preparation was local application to the oropharynx of 2% Prontocain, and 100 mg. of Demerol intermuscularly.

The gastroscope used was the Cameron-Schindler standard flexible scope. The leading flexible rubber tip of the scope had previously been injected with an emulsion of barium along its entire central longitudinal axis to assist in identifying its position on the roentgenograms.

While gastroscoping, the patients were placed on the x-ray tilt table in order to facilitate the roentgenographic examination, and to coordinate both pro-

ccedures because of the careful timing which was necessary. Both patients were scoped in the left recumbent position, and every effort was made to simulate as nearly as possible the usual gastroscopic technique.

The roentgenograms were taken in the postero-anterior position in the one patient, and in the left lateral position in the other patient.

RESULTS

The following photographs of the roentgenograms taken for this study, with their captions, tell the story more completely than words alone. These results are not as complete as we would like to have them, as time and timing is such an important factor in this type of examination.

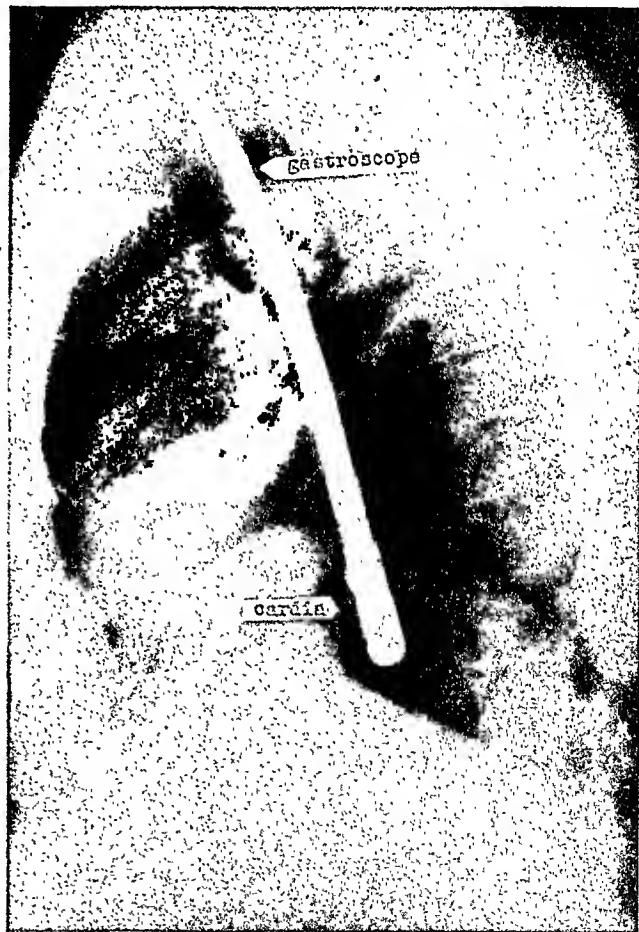


Figure 1—Roentgenogram—Left lateral position. Scope in esophagus, tip of scope entering cardia. Greatest angulation at mid-dorsal region, curvature of 10°.

COMMENTS

The analysis of this data reveals some points of interest. The greatest degree of flexion of the gastro-

scope occurs in the esophagus, and to a lesser degree in the fundus of the stomach just below the cardia.



Figure 2—Roentgenogram—Postero-anterior view. Lower 1/3 of scope shown in almost a straight line, slightly inclined to left of spine. Tip passed through cardia orifice, sharply flexed to left.

The flexible rubber tip of the gastroscope flexes acutely to the left and slightly forward as it passes



Figure 3—Roentgenogram—Postero-anterior view. Scope passed through cardiac orifice. One balloon full of air has partly inflated the stomach just sufficient to visualize a part of the midportion of the stomach. The extreme tip clings to the anterior wall of the stomach and is flexed in about the position as it was when passed through the cardiac orifice.

through the hiatus esophagus into the cardia. The flexible shaft of the scope almost completely eradicates the normal angulation of the lower esophagus and

cardia, but in compensation for this the shaft of the scope is flexed slightly at a 5° angle, with the lower half of the flexible shaft slightly inclined anteriorly.

After the objective end of the scope has passed the cardia and sufficient air has been inflated to permit separation of the walls and release of the flexible tip from the anterior wall near the greater curvature, the gastric mucosa becomes visible. Slowly inflating the stomach with air to allow the walls to separate, the scope can then be passed down to its greatest depth (Position I) for viewing the angulus, antrum and pylorus. In this lower pole of the stomach the flexible rubber tip of the gastroscope is flexed acutely and conforms quite well to the natural contour of the greater curvature of the stomach and its adjacent anterior wall. The flexible



Figure 4—Roentgenogram—Left lateral position. More air has been inflated into the stomach, and the scope is now well inside. The flexible tip and metal end of the scope rests gently against the posterior wall and greater curvature. The position of the scope permits a view of the lesser curvature and anterior wall. The midportion of the scope is bent at almost a 10° curve.

shaft of the gastroscope lies in close apposition to the posterior wall of the stomach throughout its pars media and in practically a straight line.

The blind spots or areas in the gastric wall are those parts which are in contact with or short of the focusing distance from the objective or inclined away from the objective at such an oblique angle that only a darkened area can be seen. These areas are shown clearly such as where the tip end of the scope contacts the lower pole of the stomach while in position for

viewing the pylorus, as the angle of vision is at right angles to the long axis of the scope, but the lower pole can be almost entirely viewed after partially withdrawing the scope and manipulation.

The narrow strip of the posterior gastric wall in the pars media which is in close contact with the scope, as well as the lesser curvature of the antrum, and the greater curvature of the fundus from the cardia to the

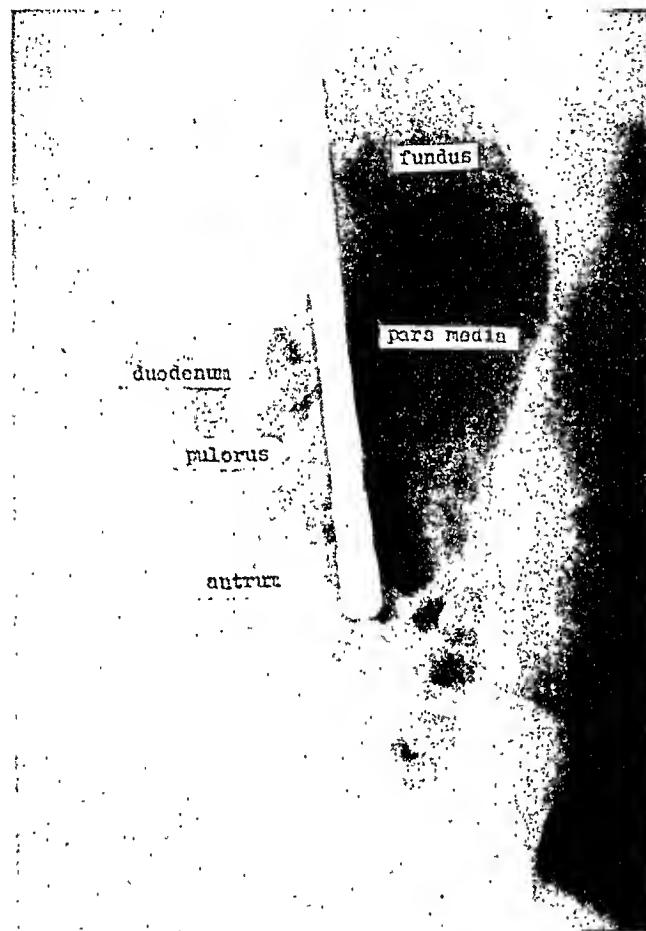


Figure 5—Roentgenogram—Modified left lateral position. Stomach fully distended with air, and the scope passed to its greatest depth (Position 1). The shaft of the scope is nearly straight throughout the entire stomach, as viewed in this position. The view through the scope shows the antrum, angulus and pylorus.

dome, are relatively too oblique in most instances, and are shown as blind or partially blind areas, as noted in the accompanying photos.

The action of the flexible gastroscope as recorded by the roentgenograms is shown to be sufficiently flexible to pass through the normal anatomical channels without any undue stress or strain. There is no roentgenographic evidence of any undue stress in the esophagus or to the adjacent mediastinal structures. In the absence of any lesion in the lower esophagus or cardia, which would prevent the proper angulation of the tip of the scope, or which would destroy the natural elasticity of these anatomical structures, there would be no danger of passage of the scope into the stomach. With proper inflation of air into the stomach, the scope can safely be passed by sight until the tip end rests in the lower pole, and here again the stomach shows a great

deal of elasticity and well compensates for the flexible end of the scope without any signs of undue pressure or strain either here or on the posterior wall.

Considerably more air than is necessary for gastroscoping can be inflated into the stomach without any great discomfort or danger, unless the walls are weakened in some particular area by a serious organic disease and rupture imminent anyway. Most of the lesser curvature, anterior wall and greater curvature of the stomach balloon out freely and permit good visualization by the gastroscope.

The air inflated into the stomach during gastroscopic examination casts an identifiable shadow on the roentgenograms, and unless eructated, flows freely from the stomach through the pylorus. (see Figure 8) which

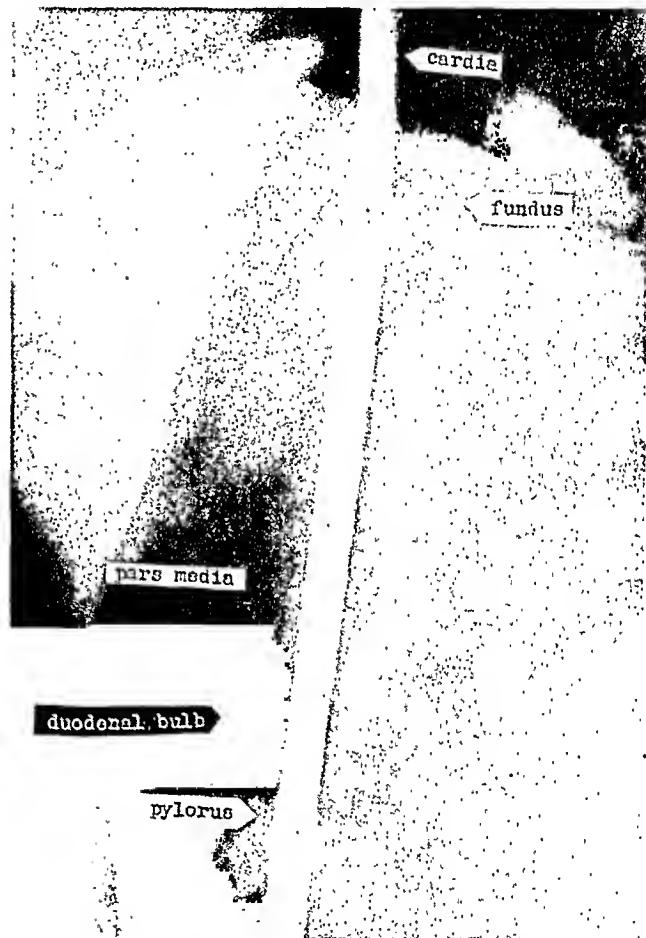


Figure 6—Roentgenogram—Left lateral position. Taken immediately following Figure 5. Scope at the same depth in viewing the anterior wall opposite angulus. The stomach is quite fully distended with air and the duodenal bulb is seen through the lower end of the stomach. The scope is curved about 5° near the cardia. The tip end of the scope rests gently against the posterior wall and greater curvature.

shows a good antral end of the stomach with peristaltic wave and a fairly good duodenal bulb.

SUMMARY

The roentgenographic investigation of the two gastroscopic examinations taken for the purpose of revealing orientation of the gastroscope in the esophagus and stomach is shown in the accompanying photographs.

The present day gastroscopic examination by the

flexible Cameron-Schindler gastroscope does not subject the patient to any appreciable discomfort or risk, if the contra-indications and proper preparation of the patient is observed. The greatest degree of flexion of the gastroscope occurs in the esophagus (10°) and to a lesser degree (5°) in the fundus of the stomach, due

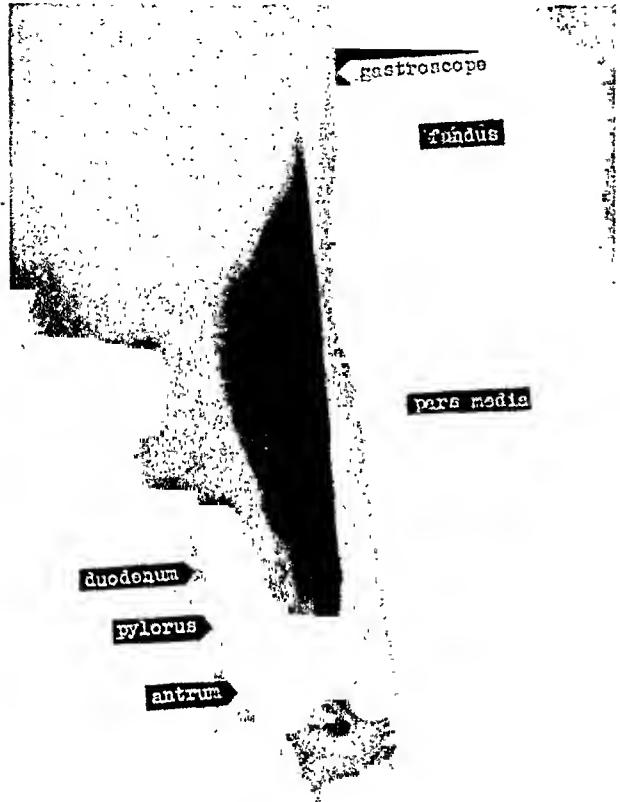


Figure 7—Roentgenogram—Postero-anterior view of air distended stomach, and scope in situ at its greatest depth (Position II). The shaft of scope is straight as viewed in this position and end is opposite angulus. The flexible tip is bent to conform to that of the greater curvature of the stomach. The gastroscopic view is that of the pylorus and antrum.

to the action of the hiatus esophagus and cardia. The cardia and lower pole of the stomach seems to be very elastic and adjusts itself to the slightest pressure of the

scope without showing any undue stress or strain. The shaft of the scope is essentially straight throughout the midportion of the stomach and lies in close apposition to the posterior wall.

The reason for the blind spots or areas of the stomach as seen gastroscopically is explained by the oblique angle of vision or short focusing distance. These can be minimized in some instances by the regulation of air in the stomach, and by manipulation of the instrument and patient. These blind areas are relatively unimportant in most cases gastroscoped, but the reason for gastroscopic failure in a few. Unless there is some modification of the present type of flexible gastroscope it will be impossible to entirely eradicate these blind areas.

It is naturally of great interest and great concern to



Figure 8—Roentgenogram—Postero-anterior view of the same stomach as in Figure 7, shows air filled lower third and pyloric orifice with partly filled duodenal bulb, without scope.

all engaged in gastroscopy to be able to visualize the entire gastric mucosa and with a minimum of risk.

In the past the pictorial action of the gastroscope was based on schematic representations and did not depict exactly what was occurring. What was felt and seen by the gastroscope gave us our orientation entirely. This study was therefore undertaken in the hope that it would facilitate a better understanding of what occurs to the gastroscope, and its effect on the anatomical structures wherein it lies.

Aluminum Phosphate Gel In the Treatment of Peptic Ulcer*

By

JACOB LICHSTEIN, M.D.**

SAMUEL SIMKINS, M.D.

and

MITCHELL BERNSTEIN, M.D.

PHILADELPHIA, PA.

INTRODUCTION

THE bulwark of the medical management of peptic ulcer in the absence of a clear cut knowledge of its etiology remains the neutralization of gastric acidity. The search for a potent agent continues to occupy the interest of clinicians and experimental workers. This interest is especially heightened by the increase of war time ulcer and the concept of peptic ulcer as a psychosomatic disease (1). To date, the aluminum hydroxide gels have considerably replaced the absorbable alkalies since it has been shown that their use does not alter the acid-base balance nor does absorption of aluminum occur (2).

Experimental data recently presented by Fauley et al (3) reveal that aluminum hydroxide gel in large doses may interfere with the absorption of phosphates in the presence of a relative deficiency of pancreatic juice, diarrhea, or a low phosphorous diet. Their studies of the effect of aluminum phosphate gel on jejunal ulcers of Mann-Williamson dogs demonstrated more decisively favorable results with this agent than with any therapeutic agents in previous use, the prevention of development of ulcer in 20 of 23 animals, and the healing of previously developed ulcers. These favorable findings led them to use aluminum phosphate gel in a small series of patients with peptic ulcer, with promising results.

Since no other clinical reports on the use of aluminum phosphate gel had appeared when the present investigation was begun, this striking healing of experimental jejunal ulcer under severe conditions prompted us to attempt an evaluation of the clinical effects of aluminum phosphate gel in the management of peptic ulcer.

MATERIAL AND METHOD

The clinical material comprised 37 unselected cases of ulcer: Duodenal, 23; gastric, 11; and gastroduodenal, 3. The patients ranged in age between 28 and 72 years, averaging 43 years. In nearly all cases the diagnosis was substantiated by roentgenograms and, where not injudicious, by gastroscopic examination. One group (Group A) of 15 patients with bleeding peptic ulcer, treated from 1934 to 1939, with various methods, (including aluminum hydroxide gel), other than aluminum phosphate gel, served as a control group. A second group (Group B) of 15 patients with bleeding peptic ulcer was treated with aluminum phosphate gel, as was likewise a third group (Group

C) of 7 patients with uncomplicated peptic ulcer.

The aluminum phosphate gel used was prepared after the method of Fauley et al (3) in a 4% solution.* The dose of the gel was 30 c.c. three times daily, after meals and at bedtime and whenever necessary during the night for the relief of pain. Treatment with the gel was begun usually on the day of admission, occasionally one to two days later, and was continued until the patient was discharged. The longest duration of treatment was forty days. In the cases treated with the continuous intra-nasal gastric drip with air-valve regulating mechanism, a 1 to 3 dilution of the gel was administered 24 hours daily at the rate of 15 drops per minute.

The diet consisted of a uniform slightly modified Meulengracht feeding (4, 5) in the group treated with the aluminum phosphate gel (fruit juices, cooked cereals, eggs, bread, milk, cream, creamed soups, rice, oysters, fish, meat or chicken, mashed and strained vegetables, custards, junkets, and puddings). With a few exceptions, as noted, the patients were begun on this diet promptly upon admission. As clinical judgment dictated, adjunctive treatment was instituted: Transfusions, cevitamic acid, iron therapy, and liquid petrolatum.

Relief of distress, healing of the ulcer as evidenced by x-ray and gastroscopy, and an increase in weight, strength, and well being were considered as criteria for improvement.

Laboratory studies included the determination of gastric analysis, blood urea nitrogen, blood calcium-phosphorous ratio, occult blood in the stools, hemoglobin and red blood cell counts, and roentgenograms of the stomach and duodenum. The effects of aluminum phosphate therapy on the above listed variables were studied.

RESULTS

GROUP A. Bleeding Ulcer Treated by Various Methods Other Than Aluminum Phosphate Gel

The average age of this group was 39 years; the youngest was 28 and the oldest 52 years. Thirteen were males and two females. The average number of previous hemorrhages was 1.4 for each patient in this group. Hemoglobin and red blood cell count on admission ranged from 22% hemoglobin and 800,000 red blood cells per mm.³ to 75% hemoglobin and 4,000,000 red blood cells, with the average at 51% hemoglobin and 2,830,000 red blood cells. The num-

* From the Medical Service of Mitchell Bernstein, M.D., Jewish Hospital, Philadelphia.

** Now serving as Captain, Medical Corps, Army of the United States.

Submitted June 13, 1944.

*The preparation used was Phosphaljel, N.N.R., kindly supplied to us by Wyeth Incorporated, John Wyeth & Brother Division, Philadelphia, Pa.

ber of transfusions required averaged two per patient. The average duration of bleeding before admission to the hospital was four days. Two patients previously had undergone surgical treatment; one a gastro-jejunostomy ten years previously, and the other a posterior gastro-enterostomy five years previously. The types of treatment used consisted of the following: Sippy progressive plus alkalies, 4 patients; Meulengracht diet plus alkalies, 5 patients; starvation, morphine and Sippy diet, 2 patients; Sippy diet plus aluminum hydroxide gel, 1 patient; Meulengracht diet plus aluminum hydroxide gel, 1 patient; Andresin diet, alkalies

ambulatory in an average of 15 days and spent 24 days in the hospital. The appetite and strength returned in full measure within 7 days. Of 14 cases studied gastroscopically, 8 were diagnosed by the gastroscopist as gastritis of various types. Two developed rather marked constipation while on aluminum phosphate therapy.

GROUP C. Uncomplicated Peptic Ulcer Treated with Aluminum Phosphate Gel

The 7 patients in this group averaged 45 years in age ranging from 39 to 72 years; 6 were males and

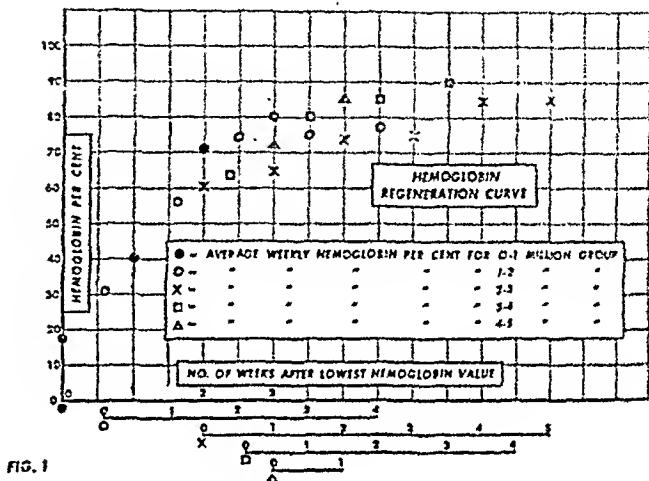
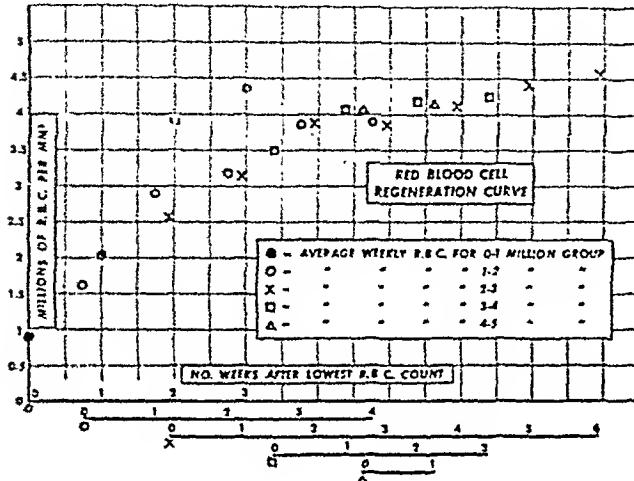


FIG. 1

and Sippy diet, 1 patient; modified ulcer diet plus alkalies, 1 patient.

The average number of days in which occult blood disappeared from the stools was 10. The patients became ambulatory in an average of 20 days following admission. Their condition was such that it was deemed necessary to administer an average of 2 transfusions of whole blood to each patient. The days spent in the hospital averaged 24, with the relief of pain or, where no pain was present, with other signs of substantial improvement in 5 days.

GROUP B. Bleeding Ulcer Treated with Aluminum Phosphate Gel

All the patients were placed promptly on a full feeding program upon admission to the hospital, with the exception of three who were given a milk and cream diet for the first few days. The 15 cases of this group averaged 44 years; the youngest was 28, the oldest 62 years. Thirteen were males, 2 were females. The average number of previous hemorrhages per patient was 1.2. The hemoglobin and red blood cell count on admission ranged from 16% hemoglobin and 900,000 red blood cells per mm.³ to 76% hemoglobin and 4,100,000 red blood cells per mm.³ with the average 57% hemoglobin and 3,010,000 red blood cells per mm.³ The number of transfusions was two per patient. The average duration of bleeding before admission to the hospital was 3.6 days.

The disappearance of occult blood from the stool occurred in an average of 6 days. The patient's became

1 female. They were placed on a modified ulcer diet and aluminum phosphate gel. The hemoglobin and red blood cell values were within normal limits as were the blood calcium, phosphorus, and urea nitrogen. Seven days, on an average, were required for the relief of ulcer pain.

GASTRIC ANALYSIS

Group B. In 4 patients, when their condition permitted, gastric analyses were done between the ninth and the nineteenth days of institution of aluminum phosphate gel therapy. Repeated analyses performed an average of 8 days later revealed a slight decrease in both free hydrochloric acid and total acidity. In 5 other patients gastric analyses (without repeat determinations) between the 4th and 27th days of treatment revealed results comparable with the above.

Group C. In 3 patients control gastric analyses checked against analyses repeated after an average of 18 days' treatment with aluminum phosphate gel showed very little change in free hydrochloric acid, but a moderate decrease in total acidity. In 3 other patients after six days' treatment, the free hydrochloric acid and total acidity determinations were practically identical with the above findings.

ROENTGENOLOGICAL FINDINGS

Group A. Of 15 patients, 1 with duodenal ulcer showed complete cure in 17 days. The remainder showed no, or very little change, by roentgenogram.

Group B. Of 15 patients, 1 with duodenal ulcer showed complete cure in 11 days, 1 gastric ulcer cure

in 17 days, and another duodenal ulcer in 2 months. One patient with duodenal ulcer showed marked improvement in 20 days, and another with gastric ulcer, moderate improvement in 12 days. The remainder who were rechecked roentgenographically within 9 to 38 days after treatment with aluminum phosphate gel was begun, showed no changes.

Group C. Of 7 patients, 1 with duodenal ulcer showed complete cure in 19 days, and another with two kissing ulcers of the fundus, cure within 3½ months. Three patients, (1 duodenal ulcer, 1 gastro-duodenal, and 1 gastric ulcer) showed very marked improvement approximately 50% decrease in size, within 11 days, 17 days, and 28 days, respectively. Two patients showed no change after 40 days of treatment.

ERYTHROPOIESIS

Erythropoiesis was expressed as the average daily increment calculated weekly from the date of the lowest red blood cell count, according to the method of Lyons and Brenner (6). The cases in Group B were arranged on the basis of the lowest red blood cell count. A glance at Table I discloses that the greater the initial anemia, the greater the average daily increment of red blood cells. In Fig. 1 the average weekly red blood cell counts for the 0-1,000,000 group, beginning with the lowest average count, were plotted on the ordinate axis and the time intervals on the abscissae. The values for the weekly red blood cell counts of the 1 to 2 million group were plotted so that the average lowest count was placed on the curve of the 0 to 1 million group. The same procedure was followed for the 2 to 3 million group, the 3 to 4 million group, and the 4 to 5 million group. The graph thus obtained had a single ordinate axis and multiple abscissal axes. Even though the number of cases represented in this series is very small, the striking coincidence of the curves obtained tends to confirm the findings of Lyons and Brenner that "the erythropoietic response of the body is determined by the degree of the anemia at the moment and is independent of the initial severity of the hemorrhage itself."

The hemoglobin percentages for the above groups, when graphed in similar fashion, yielded a curve in type somewhat similar to the red blood cell curve. The hemoglobin regeneration is more rapid than the corresponding red blood cell regeneration at lower initial levels.

The same procedure applied to Group A yielded approximately coinciding curves for hemoglobin and red blood cell regeneration.

THE BLOOD UREA NITROGEN

Group A. The blood urea nitrogen estimations determined upon entrance to the hospital averaged 23.4 mg. per cent, ranging between 12.0 and 41.5 mg. per cent. The level returned to normal within an average of 5 days.

Group B. The blood urea nitrogen on admission averaged 29.2 mg. per cent, ranging between 15.0 mg. per cent and 76.0 mg. per cent. The normal level was attained within an average of 7 days.

THE BLOOD CALCIUM AND PHOSPHORUS

The blood calcium and phosphorus values fell within normal limits in all groups. Recheck determinations in a large number of patients after prolonged treatment with aluminum phosphate gel revealed no change of note.

PAIN

Pain due to ulcer disappeared within 2 to 7 days after the gel treatment was begun in the great majority of patients. In several patients nocturnal pain was persistent, but was readily controlled by increasing the dose of the gel at bedtime, or better still, by resorting to the use of the intra-gastric drip technic. In the 3 patients in whom the drip method was employed from the very beginning, all pain disappeared very promptly within four days.

Fortunately, no mortality occurred in any of our cases and none required surgical intervention for the attack under observation.

In the aluminum phosphate treated group 8 patients (36%) were known, by follow-up of 6 months to 2 years, to have suffered recurrences. Of these 7 responded to re-administration of aluminum phosphate gel with relief of symptoms on much less intensive treatment than was previously required. Five of these patients had resorted to aluminum hydroxide gel, with only slight improvement before resuming aluminum phosphate therapy with marked clinical improvement. One patient with recurrence of bleeding ulcer responded favorably to aluminum hydroxide gel.

DISCUSSION

In almost no other chronic disease entity, in which the primary etiological factor is still in doubt, is there so much difficulty in evaluation of the efficacy of a medicament, as in peptic ulcer. The critical internist or gastro-enterologist of long experience appreciates this fact perhaps more acutely than any other observer. His intimate knowledge of the marked vagaries of the history of ulcer and the lack of absolute objective criteria for the effectiveness of a remedy in each attack, and the prevention of recurrences, make it very difficult to arrive at a valid conclusion. Criteria in this study were chosen, therefore, with the knowledge of faults inherent in each and the statistics are presented with full awareness of their possible lack of significant value.

From a roentgenological standpoint, it was difficult to evaluate the therapeutic value of aluminum phosphate gel, on account of the lack of uniformity in roentgenological diagnosis of ulcer and in evidence of healing (7). In Group A results were poor insofar as cure or improvement was concerned; in Group B results were much better; and in Group C results were excellent. One must remember, however, that many cases of ulcer heal spontaneously when the patient is hospitalized (8). However the great disparity in results obtained in Group A as compared to those obtained in Groups B and C permit the conclusion that aluminum phosphate gel was, in our series, the most effective agent employed.

Aluminum phosphate gel in the dosage employed by us produced a slight decrease in both free hydrochloric acid and total acidity. In another series of cases (8) it required much larger quantities of gel (2 tablespoonfuls every three hours and 6 tablespoonfuls at night) to reduce the volume and acidity of the gastric juice to within normal limits. It seems that the incidence and rate of healing are related to the amount of gel employed (8). This fact may account, in part at least, for the lack of success of the majority of our patients in Group B, as the dosage of gel employed by us was relatively small.

The present series confirms the work of Lyons and Brenner (6) that the erythropoietic response is conditioned by the degree of anemia at the moment and is independent of the initial severity of the hemorrhage itself. This is somewhat at variance with the conclusion reached by Schidt (9, 10, 11) that the red blood cell

series) (5), such a danger does not exist. Consequently, there is no special advantage of aluminum phosphate gel, as compared to aluminum hydroxide gel, in this respect.

Pain is very promptly controlled with aluminum phosphate gel. The chief trouble is with nocturnal pain which at times yields only to the intra-gastric drip method of treatment (7, 23, 24, 25, 26, 27, 28, 29). This is no doubt due to the greater effectiveness of this method in controlling the high nocturnal gastric acidity, commonly found in patients suffering with peptic ulcer (24).

Occult blood disappeared somewhat more promptly from the stool in Group B than Group A. It is a mistaken concept, however, to rely upon the disappearance of occult blood as an indication of the cessation of hemorrhage (4, 30, 31, 32), as it often persists for one to two weeks after the hemorrhage has ceased (33).

TABLE I

*Average Daily Erythropoiesis and Hemoglobin Regeneration**

	1st Week			2nd Week			3rd Week			4th Week			5th Week			6th Week		
	No. Cases	Rbc. Rise	Hgb. Rise	No. Cases	Rbc. Rise	Hgb. Rise	No. Cases	Rbc. Rise	Hgb. Rise	No. Cases	Rbc. Rise	Hgb. Rise	No. Cases	Rbc. Rise	Hgb. Rise	No. Cases	Rbc. Rise	Hgb. Rise
0-1 Million	1	171.4	3.4	1	257.1	4.6	1	64.3	1.1	1	1	1	1	1	1	1	1	1
1-2 Million	2	164.3	3.5	2	64.3	2.1	1	92.9	1.6	1	7.1	0.3	1	1	1	1	1	1
2-3 Million	7	89.7	2.4	7	78.6	1.1	3	16.7	0.7	2	42.7	1.2	1	28.6	0.6	1	28.6	0.3
3-4 Million	3	72.9	2.2	3	51.2	1.2	2	23.5	0.4	1	71.4	1.6	1	1	1	1	1	1
4-5 Million	1	35.9	1.4															

*Rbc rise represents the average daily increment in thousands of Rbc per m.m.³
Hgb rise represents the average daily increment in per cent.

counts of all cases following hemorrhage tend to reach 4.54 million, 33 days after the lowest red blood cell count.

It is well known that gastro-duodenal hemorrhage is followed by an elevation of the blood urea nitrogen, as was first reported by Sanguinetti (12, 13, 14). The mechanism is still not very clear (15, 16) most theories inclining to the view that the rise is due to assimilation of ingested protein, and the increase of protein catabolism (17, 18, 19). The maximum rise occurs between the 2nd and 4th day after the onset of hemorrhage, with a gradual return to normal within 5 to 7 days. The attempt has been made to relate the rise of blood urea nitrogen to prognosis, because the increase in blood urea nitrogen is a measure of the amount of blood lost (14, 20). A critical level of 30 mg. per cent is mentioned (20). In our series we had figures that ran much higher (even 76 mg. per cent), but we had no mortality.

There was no change in the blood chemistry as measured by the calcium and phosphorus (21, 22), nor was there any change in the blood urea nitrogen in the group of uncomplicated ulcers. It is only under exceptional circumstances, already cited (3) that there exists a possibility of a phosphorus deficiency with the use of aluminum hydroxide gel. For the average patient even on a Sippy diet (let alone the "Meulengracht diet" which supplies ample water, salts, vitamins, and cal-

The continued presence of blood in the stools is due to the delayed motility of the colon rather than persistent bleeding or oozing (34). In most cases it is probable that the bleeding has stopped before the arrival of the patient at the hospital (5).

We gained the clinical impression that the phosphate gel was preferable to the hydroxide gel because of its salutary effect on the appetite of the patients as well as to the fact that its constipating effect was considerably less (26).

SUMMARY

1. The effects of aluminum phosphate gel on peptic ulcer were studied in 22 patients; one group of 15 with bleeding peptic ulcer and another group of 7 with uncomplicated peptic ulcer. A third group of 15 additional patients, serving as controls, were treated with the usual ulcer regimen. The first group included 3 gastric ulcers, 11 duodenal ulcers, and 1 gastro-duodenal ulcer; the second group consisted of 2 gastric ulcers, 4 duodenal ulcers, and 1 gastro-duodenal ulcer. The third group included 3 gastric ulcers, 8 duodenal ulcers and 4 gastro-duodenal ulcers. The patients comprised 32 males and 5 females, ranging in age from 28 to 72 years.

2. Aluminum phosphate gel produced rapid marked

roentgenographic improvement and cure in a much higher percentage than did the usual ulcer regimen with or without aluminum hydroxide gel. The aluminum phosphate gel produced prompt relief of ulcer pain, had an excellent effect on appetite and return of strength, and was much less constipating than the aluminum hydroxide gel. There was a moderate reduction of free hydrochloric acid and total acidity. There

was no change in mineral metabolism as measured by the blood calcium and phosphorus, nor was there any effect on the increase of the blood urea nitrogen commonly observed in bleeding peptic ulcer.

3. The erythropoietic response following bleeding peptic ulcer is determined by the degree of the anemia at the moment and is independent of the initial severity of the hemorrhage itself.

REFERENCES

- Crohn, B. B.: Peptic Ulcer in Wartime. Editorial, Am. J. Digest. Dis., 8, 359 (Sept.) 1941.
- Kirsner, J. B.: Effect of Aluminum Hydroxide on Acid-Base Balance and on Renal Function. Am. J. Digest. Dis., 8, 160-163 (May) 1941.
- Failey, G. B.; Freeman, S.; Ivy, A. C.; Atkinson, A. J., and Wigodsky, H. S.: Aluminum Phosphate in the Therapy of Peptic Ulcer; Effect of Aluminum Hydroxide on Phosphate Absorption. Arch. Int. Med., 67, 563-578 (March) 1941.
- Meulengracht, E.: Treatment of Haematemesis and Melena with Food. Lancet, 2, 1220-22 (Nov. 30) 1935.
- Meulengracht, E.: Medical Treatment of Peptic Ulcer and its Complications. British M. J., 2, 321-324 (Aug. 12) 1939.
- Lyons, R. H., and Brenner, C.: Erythropoiesis Following Bleeding Peptic Ulcer. Am. J. M. Sci., 198, 492-501 (Oct.) 1939.
- Eads, J. T.: Clinical Results from Continuous Intra-Gastric Drip Using Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer. Am. J. Digest. Dis., 7, 32-35 (Jan.) 1940.
- Upham, R., and Chaikin, N. W.: A Clinical Investigation of Aluminum Phosphate Gel. The Review of Gastroenterology, 10, 287-297 (Nov.-Dec.) 1943.
- Schmidt, E.: Blood Regeneration in Patients with Hematemesis or Melena from Peptic Ulcer Treated with the Usual Ulcer Cure and with the Meulengracht Treatment. Am. J. M. Sci., 192, 163-167 (Aug.) 1936.
- Schmidt, E.: I. Observations on Blood Regeneration in Man; The Rise in Erythrocytes in Patients with Hematemesis or Melena from Peptic Ulcer. Am. J. M. Sci., 193, 313-327 (March) 1937.
- Schmidt, E.: II. Observations on Blood Regeneration in Man; The Influence of Sex, Age, Form of Hemorrhage, Treatment and Complications on Erythrocyte Regeneration After Hematemesis and Melena from Peptic Ulcer. Am. J. M. Sci., 193, 327-336 (March) 1937.
- Sanguineti, L. V.: Curvas azohemicas en las hemorragias retenidas del tubo digestivo. Arch. argent. de enferm. d. ap. digest. y de la nutricion, 9, 68 (Oct.-Nov.) 1933.
- Sanguineti, L. V.: Azoemias en el curso de las hemorragias retenidas a nivel del tubo digestivo (estudio clinico y experimental). Arch. argent. de enferm. d. ap. digest. y de la nutricion, 9, 264-287 (Feb.-Mar.) 1934.
- Schiff, L., and Stevens, R. J.: Elevation of Urea Nitrogen Content of the Blood Following Hematemesis or Melena. Arch. Int. Med., 64, 1239-1251 (Dec.) 1939.
- Demole, M., and Neeser, J.: L'Hyperazotemie dans les hemorragies digestives. Gastroenterologia, 64, 208-226 (Sept.) 1939.
- Stevens, R. J.; Schiff, L.; Lublin, A.; and Garber, E. S.: Renal Function and the Azotemia Following Hematemesis. J. Clin. Investigation, 19, 233-237 (Jan.) 1940.
- Kaump, D. H., and Parsons, J. C.: Extrarenal Azotemia in Gastro-intestinal Hemorrhage; General and Clinical Consideration. Am. J. Digest. Dis., 7, 189-190 (May) 1940.
- Kaump, D. H., and Parsons, J. C.: Extrarenal Azotemia in Gastro-intestinal Hemorrhage; Experimental Observations. Am. J. Digest. Dis., 7, 191-194 (May) 1940.
- Blæk, D. A. K., and Leese, A.: Nitrogen and Chloride Metabolism in Gastro-duodenal Hemorrhage. Quart. J. Med., 9, 129-149 (April) 1940.
- Chunn, C. F., and Harkins, H. N.: Alimentary Azotemia: A Clinical Syndrome Occurring as a Part of the Bleeding Peptic Ulcer Complex. Am. J. M. Sci., 201, 745-749 (May) 1941.
- Failey, G. B.; Ivy, A. C.; Terry, L., and Bradley, W. B.: An Attempt to Prevent Post-operative Jejunal Ulcer by Aluminum Hydroxide Therapy. Am. J. Digest. Dis., 5, 792-795 (Feb.) 1939.
- Woldman, E. E., and Polan, C. G.: Value of Colloidal Aluminum Hydroxide in Treatment of Peptic Ulcer; Review of 407 Consecutive Cases. Am. J. M. Sci., 198, 155-164 (Aug.) 1939.
- Einsel, I. H., and Rowland, V. C.: The Aluminum Hydroxide Treatment of Peptic Ulcer. Ohio State Med. J., 28, 173-174 (March) 1932.
- Winkelstein, A.: Studies in Gastric Secretion with a Preliminary Note on a New Therapy for Peptic Ulcer. Am. J. Surg., 15, 523-524, 1932.
- Cornell, A.; Hollander, F., and Winkelstein, A.: The Efficacy of the Drip Method in the Reduction of Gastric Acidity. Am. J. Digest. Dis., 9, 332-338 (Oct.) 1942.
- Winkelstein, A.; Cornell, A., and Hollander, F.: Intragastric Drip Therapy for Peptic Ulcer; Summary of 10 Years' Experience. J. A. M. A., 120, 743-745 (Nov. 7) 1942.
- Steigmann, F.: Colloidal Aluminum Hydroxide "Continuous Drip" in the Treatment of Large Gastric Ulcers: The Therapeutic and Diagnostic Value of This Method. Illinois M. J., 76, 443-449.
- Whitcomb, B. B.: Results from Colloidal Aluminum Hydroxide in Peptic Ulcer Therapy; An Eighteen Months' Survey at the Hartford Hospital. J. Connecticut M. Soc., 3, 272-274 (June) 1939.
- Woldman, E. E., and Rowland, V. C.: A One Flask Apparatus for the Aluminum Hydroxide Drip Treatment of Peptic Ulcer. Am. J. Digest. Dis., 8, 59-60 (Feb.) 1941.
- Chasnow, J.; Leibowitz, S., and Schwartz, R.: An Evaluation of the Meulengracht Regime in the Treatment of Bleeding Peptic Ulcer. Am. J. Digest. Dis., 7, 373-378 (Sept.) 1940.
- Graham, J. G.; Alexander, J. C., and Kerr, J. D.O.: Haemorrhage in Peptic Ulcer; Review of 241 Consecutive Cases. Lancet, 2, 727-729 (Sept. 30) 1939.
- Daniel, W. A., Jr., and Egan, S.: The Quantity of Blood Required to Produce a Tarry Stool. J. A. M. A., 113, 2232 (Dec. 16) 1939.
- Rafsky, H. A., and Weingarten, M.: Bleeding Peptic Ulcer; Clinical Appraisal of Various Methods of Treatment Based on a Series of 408 Cases. J. A. M. A., 118, 5-9 (Jan. 3) 1942.
- Hesser, S.: Über die Daner von Magengeschwüren blutungen. Acta Med. Scand. Supp., 59, 367, 1934.

Bacillary Dysentery In Curacao, Netherlands West Indies*

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UNTIL recently, the opinion prevailed that in nearly all cases, dysentery on Curacao was of amebic origin. Careful re-examination of this problem, however, has shown that the assumption is erroneous and that bacillary dysentery actually occurs frequently. The material and technic employed in the study, together with the results obtained and certain remarks concerning the problem as a whole, will be described herein.

MATERIAL

Between September 16, 1939, and December 31, 1942, a total of 429 positive cultures was produced from 2,753 samples of stool. Occasionally, causative organisms of dysentery were isolated more than once from the same case; in four cases material obtained from the colon at necropsy produced positive cultures; in one instance, five out of seven samples of urine from the same patient were found to contain the Flexner type of *Shigella paradyssenteriae*. Hence, although the total number of patients represented is 404, the total number of samples utilized actually is much larger, or 2,753. The data seen in Table I include 399 patients from whom samples of stools were obtained (sometimes more than one sample), plus the four cases in which material was obtained from the colon at necropsy, and the one patient from whom samples of urine were obtained, or a total of 404. The point is stressed that only those cases in which organisms could be agglutinated with stock serums have been included in the study. In every case but 11 the strain was the Flexner type of *Shigella paradyssenteriae*. Not once during the three and a half years represented in this study was the Shiga bacillus, or *Shigella dysenteriae*, isolated.

METHOD

For culture of the organisms Endo's medium was used until October, 1941. After that, Bacto S. S. agar was employed. The latter medium was found to produce a higher percentage of positive cultures than the former (1).

After the biochemical properties of the bacteria isolated had been determined, agglutination tests were carried out in broth cultures diluted with 0.2 per cent formalin in solution of sodium chloride. The agglutinins employed were serums obtained from Dr. A. D. Gardner, director of the Standards Laboratory at Oxford, England (2). The diluted serums and the formalized broth cultures were incubated in a water bath at 51° C.

* The Netherlands territory of Curacao, located in the Caribbean Sea, comprises the leeward islands of Curacao, Aruba and Bonaire, and the windward islands of Saint Martin (partially), Saba and Saint Eustace. The good natural harbors of Curacao and Aruba, and the proximity of the Venezuelan oil fields, have favored the construction of important oil refineries, by the Royal Dutch Shell Company, on Curacao, and the Standard Oil Company of New Jersey, on Aruba. The data reported in this paper, with a few exceptions, concern the main island of Curacao (surface area: 173 square miles; population on January 1, 1942: 68,271).

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(123.8° F.) for four and a half hours. At the end of four and a half hours a first inspection was made; the final inspection followed the next day. It was found that most freshly isolated strains were agglutinated by their homologous serums in the conventional titer of 1:250 within four and a half hours. The most efficient method for the sampling of stools consisted in the use of a cotton plugged swab fixed in a cork stopper. The stopper and swab were fitted into a test tube which contained a few cubic centimeters of diluted sterile glycerol. The swab was used as a rectal swab when it was desired to obtain a sample of stool.

RESULTS

Careful titration of 83 strains isolated showed in nine cases the presence of the Sonne type of *Shigella paradyssenteriae*, and in two cases the Schmitz type of *S. paradyssenteriae* was found. The remaining 72 strains were proved to be of the Flexner type. Application of the nomenclature of Andrews and Inman (3), Clayton and Warren (4, 5), and Boyd (6, 7, 8, 9), showed that three of the Flexner strains belonged to type V, 33 to W, three to subtype WX, two to type X, 18 to type Z, nine to the Newcastle type and three to type P119. In one case, in which the patient died, types W and Z were found together in the same sample. One type W and one Newcastle type of strain were isolated from the stools of patients living in Aruba.

It is seen, then, that nearly all serologic types of dysentery organisms are represented in Curacao, and that types W and Z of the Flexner strain of *Shigella paradyssenteriae* are the most common. It may be significant that in the Netherlands the greater part of the Flexner strains of *Shigella paradyssenteriae* belong to these two types (10). A striking difference existed in the serologic behavior of the two newer types, Newcastle and P119. If the polyvalent Flexner serum II or the homologous serum had not been used, the Newcastle strains would have been considered as inagglutinable. The affinity of the so-called P119 cultures to strains of the Flexner group was revealed by the moderate agglutination caused by polyvalent Flexner serum I. In four cases—one caused by a type W strain, one by a type Z strain, and two by a type P119 strain—positive results could be obtained repeatedly. In all instances the same serologic Flexner type was isolated for a second time.

So far as the biochemical activities of the strains are concerned, all but one (type P119) left maltose unaltered within a period of 24 hours. The indol test, performed with a 1 per cent solution of bactopeptone by the addition, after 24 hours, of equal volumes of a saturated solution of potassium persulfate and para-dimethylaminobenzaldehyde, was positive in respect to all

type V, X, Z, and P119 strains, and was negative in respect to all Newcastle cultures. Variable results were obtained with types W and WX; 22 type W strains gave positive and 12 gave negative results, whereas, of three WX strains, one gave a positive result.

The serologic Newcastle type comprises strains which produce widely different results in fermentation tests.

thirds of which slowly ferment dulcitol.

COMMENT

In most cases dysentery on Curacao is either mild or moderately severe. It is no exception to hear that the patient has recovered clinically by the time the result of the bacteriologic examination has been reported to his

TABLE I
*Strains of Dysentery Organisms Recovered in Curacao
Between 1939 and 1942*

Year	Dysentery, cases	Organism, strain					
		Flexner		Sonne		Schmitz	
		No.	Per cent	No.	Per cent	No.	Per cent
1939	26	16	61.5	10	38.4
1940	66	52	78.7	7	10.6	7	10.6
1941	98	76	77.5	13	13.2	9	9.1
1942	214	173	80.8	29	13.5	12	5.6
TOTALS	404	317	78.5	59	14.5	28	7.0

Therefore, tubes containing different sugar nutrients inoculated with these strains were incubated for 14 days. To the usual series of carbohydrates, dulcitol agar and dextrose broth with Durham tube were added. The result of the indol test was negative after 14 days;

physician. Sometimes, blood is not observed at all in the stools, or, if it is observed, it does not persist for more than one day. The macroscopic and microscopic aspects of 100 consecutive samples sent to the laboratory are seen in Table II. In the table also are recorded

TABLE II
Results of Examination of 100 Samples of Stools

Finding	Samples, no.	Dysentery bacilli	Dysentery amebae	Typhoid bacilli	Giardia <i>lamblia</i> , cysts	Strongyloides <i>stercoralis</i>	Trichuris <i>trichiura</i> eggs
Mucus, erythrocytes, leukocytes	9	8					
Mucus, leukocytes	18	6					
Mucus	24	2					
Erythrocytes	1	1				2
Leukocytes	5	1			1		
No mucus, erythrocytes, leukocytes	43	5	1	1	2	1	2
TOTALS	100	22	2	1	3	1	4

gas was not produced from dextrose or from mannitol; and there was no fermentation of dulcitol, lactose, maltose, sucrose or rhamnose. This biochemical behavior is identical to that of a minority of type 88 strains, two

other parasites found by chance or after examination based on the suspicion that the parasites might be present. The greater part of positive cultures were obtained from stools not containing blood; occasionally even a

sample not containing blood, mucus or pus yielded organisms causative of dysentery. It is highly probable indeed that more than nine out of 100 patients at some time during their illness had bloody stools, but in a country in which dysentery is endemic, the possibility that bacillary dysentery might be present should be kept in mind in each case in which it appears that "simple acute diarrhea with fever" is the diagnosis.

In addition to patients with mild "gastro-enteritis distress" and those who exhibit classic clinical signs, patients have been observed who at the onset seem to have typhoid fever with high fever, apathy, bradycardia and moderate diarrhea, without mucus or blood in the

TABLE III
Case Fatality Rate of Dysentery in Curacao in Different Age Groups

Age, group	Patients, no.	Deaths, no.	Case fatality rate, %
Less than 1 year	49	9	18.3
1 to 6 years	53	4	7.5
7 to 60 years	277	5	1.8
More than 60 years	10	2	20
TOTALS	389	20	5.1

stools. After some days the characteristics of the stools have become "typical" of the stools common in bacillary dysentery. The prognosis in such deceptive cases is poor. At necropsy the macroscopic changes of the colon are found to be slight (11).

The contention that the case fatality rate of dysentery is greatest among persons in early youth and those in old age is confirmed by the data in Table III, which shows the number of deaths in 389 cases, sub-divided according to the ages of the patients.

On Curacao, cases of bacillary dysentery in which the diagnosis is bacteriologically confirmed certainly are far outnumbered by the cases in which the patients do not come under the care of a physician, or in which, if a physician's care is available, bacteriologic examination is not carried out. Recent investigation has demonstrated that to cases of clinically evident bacillary dysentery must be added an unknown number of cases in which infection is present without illness. In a free community such as Curacao, it is a hopeless task to search for the probable source of infection in most cases. The extensiveness of the bacteriologic work required would far exceed the capacity of this or any other laboratory.

Although it is true that the greater part of the infections are being missed, the number of cases in which bacillary dysentery is recognized during a certain period may be considered a rough basis for estimation of the total number of infections occurring at that time. In the opinion of most local physicians, "diarrhea and enteritis" prevail after the rains. Curacao has an arid climate, and in the last few years (1942 excepted), precipitation has been scanty, even in the months of Octo-

ber, November, December and January, when rainfall normally could be expected. The rain usually falls in heavy showers of short duration, and because the rocky soil cannot quickly absorb such great quantities of water, the greater part of the rain is lost into the sea. Abundant precipitation at the end of 1942 was promptly followed by an epidemic of bacillary dysentery (Table IV). With due allowance for the inaccuracy of the figures available, the real number of cases being unknown, it does not seem imprudent to conclude that on Curacao epidemic outbreaks of dysentery may be expected after rainfall.

For the explanation of a possible connection between both events some information about the disposal of fecal matter on this island is necessary. In the rural districts, and in a considerable number of the houses and huts of Willemstad, no attempt is made at sanitary disposal of human excreta. At best, excreta are collected in kerosene tins and disposed of in the sea, or are scattered on the soil. A large part of the population considers a clump of bushes on the roadside or on the coast as providing sufficient privacy for defecation. The houses of the settlements of the oil refinery and part of the houses of Willemstad are connected with a sewage system. The better houses of the rest of the community have cesspools. It is well known that dry weather, with

TABLE IV
Strains of Organisms Isolated in Various Outbreaks of Dysentery in Curacao, 1939 to 1942

Outbreak, period	Strains isolated, no.	Organisms, strains		
		Flexner	Sonne	Schmitz
November, December, 1939	21	17	4	...
December, 1940; January, 1941	57	42	3	12
November, December, 1941	33	30	2	1
June, 1942	29	22	6	1
October, November, December, 1942	94	66	18	10
TOTALS	234	177	33	24

abundant sunlight and rapid desiccation of fecal matter, is less favorable to the survival of dysentery organisms and other intestinal pathogens than the hot and humid environment which prevails after rainfall. Moreover, it is obvious that the overflowing of cesspools which occurs after a heavy shower favors the spreading of pathogens. Pollution of public wells, which constitute the common source of drinking water in the rural districts, by water leaking through fissures in the soil certainly is not impossible. This process, however, cannot have played a role in a large fraction of the recorded cases, because many of the patients consumed chlorin-

ated drinking water supplied by the government or the oil refinery.

Probably more important than the foregoing postulates is the fact that after a period of rain, the number of flies rapidly increases.

Finally, it may be remarked that the epidemics on this island (Curacao) have not been caused by one single or special type of dysentery organism, but that, as has been shown by observations made elsewhere, various types have been found to exist. The strains isolated in different acute outbreaks of dysentery, occurring from November of 1939 through December of 1942 are listed in Table IV.

REFERENCES

1. Pot, A. W.: Difco SS Agar in Diagnosis of Bacillary Dysentery. *Lancet* [London] 1: 677 (June 6) 1942.
2. Gardner, A. D., Dudgeon, L., Bulloch, W., and O'Brien, R. A.: The Dysentery Group of Bacilli. In: *A System of Bacteriology in Relation to Medicine*. London, His Majesty's Stationery Office [Privy Council: Medical Research Council], 1929, vol. 4, pp. 159-253.
3. Andrewes, F. W., and Inman, A. C.: A Study of the Serological Races of the Flexner Group of Dysentery Bacilli. London, Medical Research Committee (National Health Insurance), Report No. 42, 1919. Pp. 64.
4. Clayton, F. H. A., and Warren, S. H.: An Unusual Bacillus Recovered from Cases Presenting Symptoms of Dysentery. *J. Hyg.* [Cambridge] 28: 355-362 (Feb.) 1929.
5. Clayton, F. H. A., and Warren, S. H.: A Further Study of an Unusual Bacillus Recovered from Cases Presenting Symptoms of Dysentery. *J. Hyg.* 29: 191-200 (July) 1929.
6. Boyd, J. S. K.: Some Investigations into so-called "Non-agglutinable" Dysentery Bacilli. *J. Roy. Army M. Corps* 57: 161-186 (Sept.) 1931.
7. Boyd, J. S. K.: Further Investigations into the Characters and Classification of the Mannite-fermenting Dysentery Bacilli. *J. Roy. Army M. Corps* 59: 331-342 (Nov.) 1932.
8. Boyd, J. S. K.: A Review of the Dysentery of India, with Special Reference to Certain Recently Described Types. *J. Roy. Army M. Corps* 66: 1-13 (Jan.) 1936.
9. Boyd, J. S. K.: The Antigenic Structure of the Mannitol-fermenting Group of Dysentery Bacilli. *J. Hyg.* 38: 477-499 (July) 1938.
10. Pot, A. W., and Dornickx, G. J.: Uit Klinik: Bijdrage tot der inheemsche dysenteriebacteries. *Geneesk. gids*. 11: 501-513 (June 2) 1933.
11. Pot, A. W., van Raalte, H. G. S., and van der Sgr, A.: Bacillary Dysentery in Curaçao. *Geneesk. tijdschr. v. Nedrl.-Indië* 82: 234-250 (Feb. 10) 1942.

SUMMARY AND CONCLUSION

On Curacao, bacillary dysentery is one of the most frequent contagious diseases. In most cases the disease is either mild or moderately severe. After significant rainfall, epidemic outbreaks may be expected. Nearly all serologic types of the Flexner strain of *Shigella paradyssenteriae*, as described by Andrewes and Inman in 1919, were recovered; type W was most often found. Next to these so-called older types, strains were isolated which were identified as the Newcastle type and the type P119 of Boyd. The Shiga bacillus or *Shigella dysenteriae* has never been found.

It is concluded that the causative agents are the Flexner, Sonne and, to a lesser degree, Schmitz, strains of *Shigella paradyssenteriae*.

Gastrointestinal Disorders Simulating Circulatory Disease and Vice Versa*

By

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THE diagnostic difficulties, often encountered, in determining the origin of certain pathologic signs, in particular pain sensations, are well known to every physician. Nothing is more dangerous than to make a diagnosis by hard and fast rules, at least as long as one is not aware of, nor considers carefully, the exceptions, variations and common sources of error.

This is often experienced in patients suffering from circulatory or gastrointestinal disorders. In both instances the subjective symptoms can and often do lead one astray.

There are three possibilities: (1) Both organs may be diseased simultaneously, (2) a gastrointestinal disease may simulate heart disease, (3) a disease of the circulatory system may be concealed by gastrointestinal symptoms.

Not infrequently, of course, *both systems can be diseased simultaneously*.

Case 1. G. R., Male, aged 55, family history negative. Smoked 40 cigarettes a day. Wasserman neg. Appendectomy at age of 25. For many years suffered from symptoms indicating stomach ulceration. At age of 38, gastroenterostomy was performed. The digestive complaints continued, however, and 12 years later, the stomach was resected. In spite of this he continued to suffer from pains between the shoulder blades and in the upper abdomen. He returned for the third time to the same Surgical Institute where gastroscopy revealed an ulceration on the scar of the previous operation. Because he had suffered from an attack of tachycardia a short time previously, the heart was also examined and was found to be healthy. A few months later he suffered an acute coronary occlusion with all its clinical findings. Even after the heart attack the roentgenogram of the heart was normal. No signs of pathologic circulatory conditions persisted with the exception of marked electrocardiographic changes. We therefore may assume that coronary changes were already present before the stomach was resected and that the patient suffered from two diseases. (See Fig. 1).

The presence of both gastrointestinal and circulatory disease is not so frequent, that one must necessarily conclude, that both are always the consequence of one and the same pathologic condition. Taking into con-

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sideration the many heart cases I have seen, many of whom have had their gastrointestinal tracts carefully examined, it seems to me that gastrointestinal disease is not more frequent amongst heart cases than amongst other patients.

Nevertheless one cannot deny that if coronary thrombosis and gastrointestinal ulceration were present in the same case, (as in Case 1) the pathogenesis may be a common one.

For more than twenty-five years *von Bergmann* (1) stressed the important role played by the vegetative



Figure 1—Case 1

nervous system in the etiology of gastric ulcerations, and even more so in cases with symptoms of ulceration without positive findings—ulcus disease without ulcus as he called them.

In regard to angina pectoris, *Heberden's* (2) view has always been accepted, that alterations or variations in the tone of the autonomic nerve system, mainly the vagotonic type characterized by low blood pressure, bradycardia, pale complexion—can cause the symptom angina pectoris and may predispose to the development of true coronary disease. It is evident that in areas in which the arterial supply is moderate (3, 4), or relatively inadequate in relation to the functional stress laid upon these areas, acute disturbances in blood supply may easily lead to functional and even occasionally to organic disturbances. On the other hand there are similar areas in which such sequelae are missing.

The extremely stormy and diagnostically confusing results of an overstimulation of the autonomous nervous system may be seen, for instance, in certain cases of cardiospasm with angina pectoris. I have seen several patients suffering from occasional nocturnal attacks of excruciating pain, deep in the chest with distinct "globus sensation", fear of swallowing, fear of breathing deeply, cold extremities, perspiration, and so on. The attack concluded finally with voluminous urination. The pain in the chest persisted for one to two days, gradually becoming milder.

Case 2. Mr. Schw., 45 years old, suffered all his life from frequent violent nightmares. At longer intervals, but occasionally several times during a week, he was awakened between 3 and 6 A.M. by terrific pains in the chest; in addition he had dysphagia, air hunger, profuse perspiration, cold extremities, et cetera. After some time he had diarrhea and copious urination. Thereafter the pain gradually disappeared during the next 12 hours. Repeated thorough examinations failed to reveal any abnormalities.

Since, as mentioned before, the number of patients suffering simultaneously from diseases of the two organs is comparatively scarce, one may assume, that the systemic disease—the disturbance in the autonomic nervous system—leads only to one or the other, or to several organic diseases if one or several additional pathologic factors coincide. In other words the simultaneous appearance of circulatory and gastrointestinal disease is a question of chance. The reports of *Levy and Boas* (5) do not seem to me to contradict this view.

Case 3. E. G. Male, aged 45, a cook, Insignificant history. He suffered the first stenocardial distress two years ago. His weight was reduced from 214 to 185 lbs. However, the symptoms persisted. Careful examination of the heart a few months ago was negative in every respect. Under treatment the condition improved, until the patient overexerted himself greatly and the stenocardia returned. The cardiological findings were again absolutely negative. While questioning the patient once more he stated that for fifteen years he had been under observation for suspicion of gastric ulceration. Occult blood examinations had been occasionally positive in stool and stomach contents, but repeated x-ray examinations were negative. This then is a case in which, on a neurogenic basis, the symptoms of angina pectoris and those of gastric ulceration occur simultaneously whereas careful examination of both organs failed to lead to a definite diagnosis.

In other cases the long existing disease becomes complicated years later by a disease of a second organ.

Case 4. J. H., Female, aged 42, has two healthy children. About 8 years ago a diagnosis of heart disease was made. She was decompensated for 6 months. One and one-half years ago she developed signs of decompensation again and also auricular fibrillation. Shortly thereafter she suffered an attack of acute rheumatic fever. While in bed a cerebral embolism occurred. Since then she has had frequently embolic episodes in the kidney, liver, et cetera. The liver attacks however were according to the family physician of different types. In one instance the chill followed the attack of pain, in another the chill preceded the attack of pain. When I saw the patient she presented all the signs of cholecystitis with a high degree of jaundice, tenderness in the gall-bladder region, et cetera. There can be no doubt that this patient suffered alternately from minor abdominal emboli and from attacks of cholecystitis.

What was mentioned regarding the possible mutual etiologic basis of coincident heart and gastrointestinal affections explains in greater part what not infrequently happens, namely that *gastrointestinal disease leads to the erroneous diagnosis of heart disease*. The pathologic condition of the autonomic nerve system in such cases may form the basis for the gastrointestinal organic disease and may simultaneously lead to functional but not necessarily to organic disturbances of the heart.

Such cases are understandable, however, only if one remembers that autonomous reflexes radiate from one organ to the other. Our knowledge regarding the radiation of autonomous reflexes is more than 80 years old. I mention only the experiments conducted in 1863 by *Goltz* (6), who caused cessation of the heart beat in the frog by rhythmic tapping of the stomach. *Bruno Kisch* (7) in recent years has made many contributions con-

cerning the radiation of autonomous reflexes. There have been innumerable publications showing the various paths of reflex radiation between the abdominal and circulatory systems. For a closer study of this matter, I recommend the book written by a Fellow of the Kerckhoff Heart Research Institute, *Alfred Schatzker* (8).

All cardiac symptoms can be caused or simulated by gastrointestinal disease. I mention only tachycardia, especially paroxysmal attacks, extrasystoles, dyspnoea after meals as a consequence of the elevated diaphragm and, most important, angina pectoris. I could cite many cases in which the cardiac complaint disappears after the ulcer or other abdominal disease, even cancer, was in one way or the other cured.

I mention only Mr. S. who was operated at the age of 44 for a duodenal ulcer and Mr. S., also operated for cancer of the pylorus at 63, and Mr. G. who was operated at 54 for a cancer at the pylorus. They were free of stenocardia for years after the operation, the latter for ten years.

Affections of the oesophagus often simulate heart disease, primarily coronary disease. There are many patients with oesophageal diverticuli, by whom a diagnosis was only arrived at, after the heart examination had failed to explain the cause of the subjective symptoms or after long ineffectual heart treatment. This also holds true for oesophageal carcinoma.

Case 5. F. S., Female, aged 72, never ill nor operated. For the last 8 months suffered from dizziness, pain in the shoulders radiating into the chest and arms. B. P. 170/80. Rough systolic murmur audible over precordium, and the heart distinctly enlarged. Treated as a hypertensive case. The patient also complained of dysphagia. X-ray examination revealed the presence of an inoperable carcinoma of the oesophagus.

It is often extremely difficult to decide whether a chronically enlarged liver, perhaps with a rough surface, is the sign of an abdominal disease or the consequence of circulatory disturbance. In many cases it is necessary to x-ray the gastrointestinal tract in order to exclude the possibility of malignancy or metastases. Even this, however, may not always lead to a clarification of the situation, as was demonstrated in one case recently observed, where the cancer was hidden in the liver and could not be clinically proven.

Case 6. Mr. V. D., had been under treatment for 8 months heart disease because of general anasarca, ascites, hydrothorax, and edema. The last mercaptozin injection resulted in amnesia and unconsciousness. He was therefore taken to the hospital. A definite diagnosis could not be reached. However, even though the patient had imbibed considerable quantities of alcohol, the enlarged liver with very rough surface made us suspicious of a malignancy; but it could not be located. At the postmortem examination cancer of the liver was discovered beneath the diaphragm; it had grown into the inferior vena cava and extended into the right auricle. Thrombus formation had finally occluded both kidney vessels.

There are numerous cases in which the formation of gastrointestinal diverticuli simulates angina pectoris.

Case 7. Mrs. v.d.B. This lady was observed over a period of 30 years and treated for 15 years as a case of neurogenic angina pectoris. Fifteen years ago I saw her for the first time during an attack which I diagnosed as one of diverticulitis. X-ray examination showed a very extensive diverticulosis of the colon. Henceforth the patient was treated repeatedly for such attacks, and in between for attacks of angina pectoris. She developed signs of increasing cerebral

arteriosclerosis and died past 80 years of age from cerebral arteriosclerosis.

This case demonstrates what I have in general found to be true, namely, that these cases die in the seventh or eighth decade of an intercurrent disease.

In differentiating between stenocardial and gall bladder pain one often encounters considerable difficulty. It has already been shown in the case report No. 2 that in cardiac patients liver emboli may alternate with attacks of cholecystitis.

Cases in which the final operation upon the gall bladder leads to a prompt and permanent relief of circulatory disturbance, erroneously diagnosed as angina pectoris are frequently seen.

Case 8. W. K., Male, was seen for the first time by me 20 years ago. Although his family physician reported that the patient had suffered an attack of coronary occlusion, his heart was in good condition. I saw him at intervals and never found anything wrong with his heart. In 1936 I observed an attack. The blood pressure was definitely higher than usual. The electrocardiogram taken during the attack showed a prolonged conduction time, but the clinical picture was that of a gall bladder attack. A surgical consultation confirmed the diagnosis. However, the family physician maintained his diagnosis of coronary insufficiency. The same situation recurred a few times. Then, while the patient was on a cruise in the south seas, I received a telegram from the ship's physician asking for advice and stating that Mr. K. suffered from a coronary occlusion. I recommended treating the case as one of cholecystitis. A few days later I received another telegram saying that the patient had been transferred to a hospital in Havana for a gallbladder operation. I insisted that he should return to New York, which he did. An operation revealed a completely shrunken gall bladder which was removed. In the meantime the patient has also undergone a transurethral prostatectomy and during the past years the man, who is now 75 years old, has enjoyed perfect health. His ECG. and his blood pressure have returned to normal. The temporary pro-

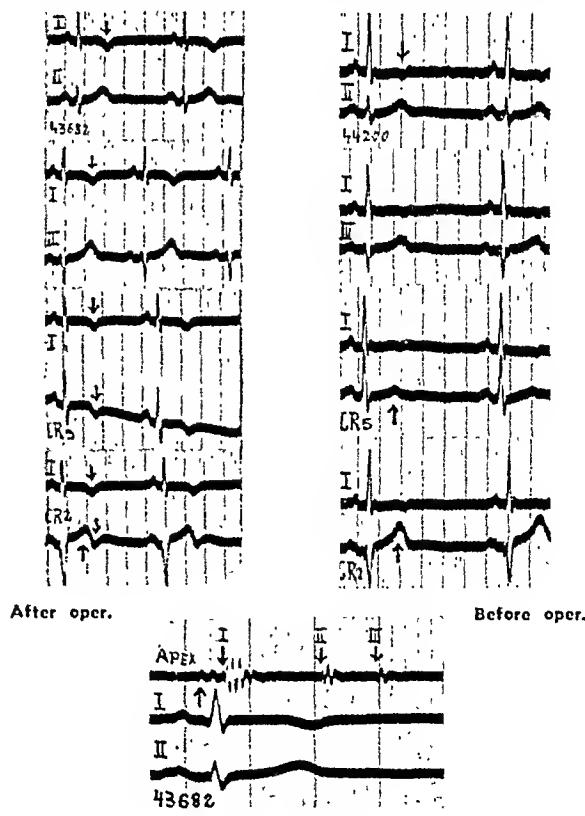


Figure 2—Case 9

longation of the conduction time may, with good reason, be attributed to a toxic condition during the cholecystitis.

Case 9. Dr. K. thirteen years ago suffered from a severe tonsillitis. Since then he has experienced attacks of tachycardia, once a meningitis, and twice otitis media. Years ago he had occasional pain in the gall bladder region. In 1939 an ileus-like attack occurred. X-ray pictures were negative. Recently, however, the gall bladder was not visualized on x-ray examination. A few months ago when his stenocardial distress became increasingly worse, he consulted me. Physical examination revealed a gallop rhythm and a distinctly enlarged heart. The Ecg. showed a sharply inverted T in lead I and an inverted T in lead CR-5. I recommended gall bladder operation, despite all other colleagues' opposition. However, the removal of the highly dilated and infected gall bladder was performed and recovery was uneventful. Since then the patient has fully recuperated. He no longer has any stenocardial distress and no gallop rhythm. His blood pressure, which was slightly elevated before, became normal. The T-wave in Lead I became less sharply inverted and in Lead CR-5 upright one week after the operation. (See Fig. 2).

Such cases suggest that gall bladder disease may predispose to myocardial and arterial degenerative changes, and that both conditions may, occasionally, be due to a common cause, namely a focal infection. The first focus may, for instance, be situated in the tonsils, the second in the gall bladder.

Stone formation in the gall bladder frequently leads to pain sensations in the chest. I have found this more often in the presence of a big solitary stone than with many smaller calculi.

Case 10. M. H., Male, now 75 years old, suffered for 12 years from occasional anginal attacks and was treated as a coronary case. The diagnosis cholelithiasis was made only after several years. The patient was treated conservatively. From time to time he has very mild gall bladder attacks, as well as frequent mild stenocardial distress. However, since his Ecg. and the other clinical findings were constantly normal, operation was deemed unnecessary.

explanation for the coincidence of cardiac and gastrointestinal disease, namely, metabolic abnormalities.

Particularly interesting and important from the diagnostic standpoint are those patients suffering from angina pectoris, but who have only diaphragmatic anomalies. Recent literature contains a constantly increasing number of reports on cases with diaphragmatic herniation in which the diagnosis only becomes possible by means of roentgen rays.

Case 11. R. S. W. First seen at the age of 77 years. Examination revealed an hypertension with attacks of auricular flutter. Her heart shadow was greatly enlarged, extending to the left axillary line and, as it seemed, surpassing the right midclavicular line. According to previous examinations part of the right side of the heart shadow was attributed to repeated pleural transudation. By means of quinidine the heart action became temporarily normal, the conduction time however appeared prolonged, no doubt the consequence of arteriosclerotic changes. When the patient died a few months later the autopsy showed, besides myocardial degeneration, a para-sternal diaphragmatic hernia extending into the right pleural cavity and covered by pleuritic scar formation. This contained a loop of transverse colon, part of the greater omentum, et cetera. The heart was displaced to the left. The case is fully described by *R. A. Colmers*. (10)

One cannot deny that in cases of diaphragmatic hernia, because of "too little space" the heart easily becomes damaged. Even a high degree of chronic elevation of the diaphragm may cause circulatory disturbances. A typical case is to be found in the *Lehrbuch und Atlas der Roentgendiagnostik* (11).

More frequent and important are those patients suffering from hiatus herniae. Our interest in these patients was first stimulated by *Akerlund* (12). Up to that time only 60 cases had been reported in the literature. Akerlund added 24 cases that came under his observation, proving that the instance of hiatus hernia is much higher than was generally supposed. Since then publications by many physicians and clinics concerning congenital as well as acquired or traumatic herniae have appeared. (*Harrington* (13)).

Murphy and Hay (14) came to the conclusion that anemia is so commonly associated with hiatus hernia that "its presence may be logically explained on the basis of the hernia and it must be considered an important aid in the diagnosis." This statement seems to me to be erroneous. Only in the late stage when incarceration symptoms occur can bleeding and anemia be expected. *Sahler and Hampton* (15) surveyed the literature concerning bleeding in hiatus hernia. Among their own cases (a series of 221 patients with marked hernia, beginning herniation not included) only 14% had "either moderately marked anemia or a positive history of gastrointestinal tract bleeding." This is in accordance with our own experience.

Hiatus hernia lacking a distinct symptomatology, is not only very difficult to diagnose, but also leads not infrequently to false diagnostic conclusions. It is, as often stated, "the masquerader of the upper abdomen" (16).

Akerlund's differentiation of three types of hiatus herniae is generally accepted:

1. Hernia due to a congenitally short oesophagus. In such cases part of the stomach is above the dia-

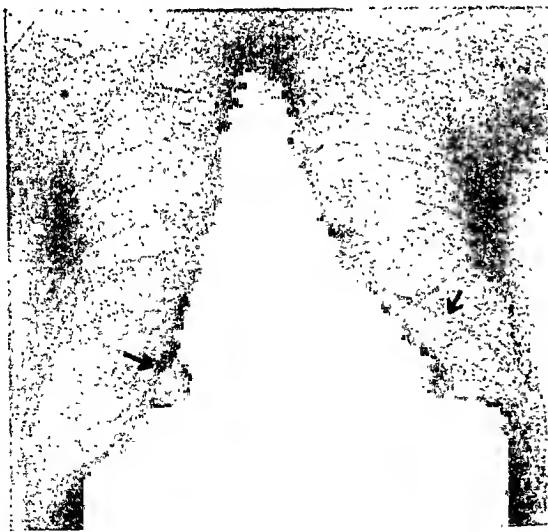


Figure 3—Case 14

Cases like the latter probably belong to the reflex angina pectoris group. They may, however, as *Bramwell and King* (9) state, start on a mutual basis, namely an abnormal cholesterol metabolism. Statistical studies have not been convincing since both diseases are very common. Such cases, however, present a possible

diaphragm in the thoracic cage forming a "thoracic stomach", a "cow stomach", or "Vormagen".

2. The para-esophageal type with incomplete or weak closure of the diaphragm and congenital or acquired herniation of intestinal organs through the hiatus esophagaei.

3. The gastro-esophageal type with upward displacement of the stomach together with the oesophagus.

A fourth group has to be added in which the oesophagus is of normal length and the stomach in its normal position, but parts of the ileum and the colon are herniated.

Only the first variety, the thoracic stomach due to a short oesophagus, is necessarily a chronic condition. The other types, according to my experience, may be temporary and only in later stages chronic and may lead finally to incarceration.

All varieties of hiatus herniation exist for many years without symptoms. If not accidentally discovered, they usually cause subjective symptoms, when temporary or chronic incarceration occurs, thereby causing attacks of pain when the vagal nerves, which enter the abdomen through the hiatus oesophagaei, are compressed or pulled. *Von Bergmann* (17), and his co-workers studied this particular phase of the problem experimentally in animals.

Such irritation of the vagal nerve may lead in one case to stomach symptoms, in another to heart symptoms, and still in another to a mixture of both symptom complexes. In regard to vagal irritation and its consequences upon the heart, we know that it can lead to a narrowing of the coronary arteries and temporary coronary insufficiency, which in turn produces the clinical picture of angina pectoris.

We fully agree with *Wiggers* (18) who in discussing the differential diagnostic difficulties of "heart aches" says that, "many have their origin in the lower oesophagus and cardiac region of the stomach, which seem to respond readily to emotional and irritable states of the subthalamic or hypothalamic regions. Others are perhaps suggestive of organic disturbances such as diverticular dilatations, etc. This, however, does not exclude a cardiac origin, at least in some patients and this despite the fact that the pain may not be affected by effort but seems to be intensified by indiscretions in diet, etc."

Case 12. M. K. G., Female, is one of the striking examples. She is now 62 years old. In childhood she suffered from asthma and other muscular spasms, for instance at the sphincter ani. After the husband died from severe coronary sclerosis and one of her daughters, who suffered from dementia praecox, had killed herself, the patient developed a most severe angina pectoris. The regular periodic examinations between 1920 and 1930 were always normal. The gastrointestinal tract including the oesophagus was negative. Nitroglycerine gave her relief. Higher altitude—perhaps of significance—improved the condition. The blood pressure was always low. Six years ago she wrote from South Africa, stating that the pain had changed in type, had become almost unbearable, and that she found some relief only by leaning against something or stretching. When she came to the United States eighteen months ago a typical hiatus hernia with incarceration at the hiatus and ulcer in the fundus was found. The blood pressure was normal; the second aortic sound accentuated. The Ecg. showed left axis deviation. Phrenic nerve ligation brought relief.

Case 13. K. K. He was 60 years old when he came under observation. Nothing of interest in the history. Five years previously he had had an attack which was taken to be a kidney attack. However, the kidneys were later found to be normal. At about the same time his blood pressure was found to be very high and he was rejected for life insurance. His blood pressure varied between 250 and 200/150-130. He had shown pronounced scoliosis since early childhood. His main complaints were shortness of breath, ringing in the ears, bloated feeling and heart burn. His heart and aorta were distinctly above normal in size. The Ecg. was of the left axis deviation type. When I was consulted for the first time I found that he suffered from a bronchitis with elevated temperature. The lateral x-ray of the chest showed a big air bubble just above the diaphragm and behind the heart. Further x-ray studies led to the diagnosis of an incarcerated hernia, probably with ulcer formation in the incarcerated stomach, and with subsequent pleurisy. Occult blood was present in the feces. Thoracentesis revealed hemorrhagic transudate. The blood count changed rapidly until the hemoglobin reached 25 per cent and the red blood cells 1,500,000. Operation was impossible. The patient bled de facto to death, while his blood pressure remained constantly above 200.

Case 14. N. Schw., Male, 64. Outside of bilateral inguinal hernia nothing of interest in the history. He complained of gas and stenocardial distress. All the cardiac findings were negative. The x-ray of the chest showed the heart to be approximately normal in size; the heart shadow was crossed by a circular linear shadow extending from the left costodiaphragmatic angle to the middle of the right diaphragm and revealing a shadow above both diaphragmatic domes, terminating upwards with a horizontal line. The lateral roentgenogram showed a large oval shaped body behind the heart which was filled with air in its upper part, and with fluid in the lower; the whole pushing the oesophagus backwards. By accurate and detailed



Figure 4—Case 14

examination it was found that the contents of the herniation consisted of small bowel. (See Fig. 3, 4 and 5).

It has been shown how often heart symptoms can conceal an abdominal disease. The contrary, namely that a *disease of the circulatory system is hidden by gastrointestinal symptoms*, is no less frequent.

Dyspepsia, hyperacidity, belching, distension of the abdomen, flatulence, nausea and colitis are treated in hundreds of cases for many years before their cause—the heart disease—is recognized. All the foregoing and

many more symptoms of dysfunction of the gastrointestinal tract are often the first signs of diminished or poor circulatory function, of venous stasis, of hyperemia of the mucous membranes, et cetera. It is needless to report examples here.



Figure 5—Case 14

The angina pectoris patient, however, requires special mention. In many cases the patient reports as follows: for years I suffered from dyspepsia (or from eructation after eating, or from heart burn). Only when I suffered the attack, which the doctor told me was a heart attack, did I understand that all these years it had been my heart which bothered me. Many patients who feel discomfort after meals in the region of the lower 1/3 of the sternum are relieved by eructation. Thus it is not astonishing that they hold the stomach responsible for the condition. Every big meal leads, as we know, to a shift in the distribution of the blood, emptying certain blood reservoirs and filling others. We may, therefore, call angina pectoris appearing after meals an effort symptom.

In other cases heart burn after meals or even on an empty stomach is the main complaint. Certain food is often claimed by the patient to cause it. Frequently, to mention only one example, coffee is held responsible for it. Then the patient abstains from coffee, or whatever it may be, for a while and feels relieved, but after a short time the heart burn returns and now returning to the same food, for instance from tea to coffee, again brings relief.

For decades all these questions were discussed in the literature as the "gastro-cardial syndrome". It is, however, not possible to blame hyperacidity for angina pectoris. It is more logical to assume that both are the consequence of the same neurocirculatory disturbance. We likewise cannot assume that gaseous distension—at least within physiologic limits—causes angina pectoris. The numerous experiments performed on animals and students are not convincing. Here, too, neurocirculatory

disturbance leads to a simultaneous reaction on the different organs. It is, by the way, true that the majority of angina pectoris sufferers swallow air, when they have once experienced that eructation gives them relief, and not that the air originates in the stomach.

Case 15. W. M., Male, 68 years of age, always over weight, extremely active, suffered for years from severe heart burn and was treated for it. A few days before I was consulted, after having chopped down a few trees, as he said, he felt an extremely severe heart burn. After dinner he called in a physician who made a diagnosis of angina pectoris. For the next 24 hours he suffered repeated attacks. An Ecg. taken at once showed a right bundle branch block. This Ecg. was similar to tracings taken three years and one year before, on the occasion of a general check-up, demonstrating that the condition had existed for at least three years.

Case 16. J. M., Male, aged 74. Suffered for many years from hyperacidity, distension of the abdomen, eructation, etc. During the last 6 months he experienced pains more frequently, radiating from the stomach into the arms. He had, however, similar pains since 1941. He was examined occasionally and Eegs. were taken. The limb leads of the electrocardiogram, except for a slight notching of the S-waves, were normal. The chest leads showed a typical right bundle branch block. No doubt the patient had suffered from angina pectoris for at least three years. He continues to believe that gas formation is the cause of his ailment. (See Fig. 6).

We mentioned the diagnostic difficulties often encountered in patients with enlarged livers. It may be advisable to remember that enlargement of the liver is often the first sign of constrictive pericarditis.



Figure 6—Case 16

Case 17. C. P., Male, was 45 years old when I first saw him, and at which time he reported that he had been treated during the preceding five years for gastric ulcerations and that he also had suffered from attacks of palpitation. Ecg. revealed a slowly fibrillating heart with occasional superimposed attacks of tachycardia. Physical examination revealed a gallop rhythm and the liver edge was palpable more than four fingers below the costal margin. Roentgen examination in the dorso-ventral diameter showed the heart to be slightly above normal in size; the ascending aorta was somewhat widened. The lateral view, however, showed in addition to the slight enlargement of the auricles a dense shadow encasing the ventricles proving that the patient suffered from a calcified pericarditis. (See Fig. 7).

Not infrequently a patient is treated for heart disease only because of dyspnea. When hydrothorax subsequently develops and the heart medication fails, signs of intestinal obstruction may appear and the roentgen examination may finally show, that the patient suffered all this time from intestinal carcinoma with metastases to the pleura.

Abdominal emboli very often cause the greatest difficulties in differential diagnosis, especially when the existence of a heart lesion is unknown, or—as in patients suffering from mitral stenosis—is overlooked. Even operations are occasionally performed because of such quite understandable errors.

In this connection aneurysms of the abdominal aorta should be mentioned. The clinical signs of this not uncommon disease are so indistinct that—as I have observed in two cases (19)—only most careful x-ray examination can substantiate the diagnosis during life.

Case 18. The main complaints of the 72-year-old patient were nausea and some shortness of breath. Only because the heart findings were not impressive and because he complained of chronic nausea and loss of weight his abdomen was examined by means of x-ray and a calcified abdominal aneurysm, later on verified by autopsy, was revealed.

It is important to remember that an abdominal aneurysm may simulate an abdominal disease, as demonstrated by Osler (20) who reports "two such cases in which operation was performed."

I have seen one case in which the surgeons insisted on an operation and autopsy proved the roentgenological diagnosis for an abdominal aneurysm. The patient died however before the operation and autopsy proved the roentgenological diagnosis.

I cannot conclude without mentioning the fact that constant nausea in a patient with heart disease, especially encountered in those with enlarged livers, often worries the physician and leads him to believe that an abdominal disease may be present as well. Temporary discontinuation of the heart medication, especially of digitalis, usually brings relief and clarifies the cause of the nausea. Changing thereafter the method of application of the drug leads to more satisfactory therapeutic results. We must also remember that the drugs of the xanthine group may, after long use, cause watery bowel movements.

SUMMARY

1. Gastrointestinal and circulatory disease may be present simultaneously. In such instances the pathogenesis of both may be a common one, namely (a) disturbance in the autonomic nerve system, (b) poor blood supply in certain areas, (c) focal infection.

2. In patients with gastrointestinal disorders, heart disease may develop as an independent second disease and vice versa.

REFERENCES

1. v. Bergmann, G., *Funktionelle Pathologie*. Springer, Berlin, 1932, 31-57.
2. Heberden, W., *Commentaries on the History and Cure of Diseases*, Boston, Wells & Lilly, 1818, p. 296.
3. Reeves, T. B., Study of the Arteries supplying the Stomach and Duodenum, and their Relation to Ulcer. *Surg. Gynee. & Obst.* 30, 374, 1920.
4. Jatrous, Ueber die arterielle Versorgung des Magens und ihre Beziehung zum Ulcus Ventriculi. *D. Ztschr. i. Chir.* 159, 196, 1920.
5. Levy, H. and Boas, E. P., Angina pectoris and the Syndrome of Peptic Ulcer. *Arch. of Int. Med.* 71, 301, 1943.
6. Goltz, Fr., Vagus und Herz. *Virehov's Archives*, 26, 1, 1863.
7. Kisch, Bruno, Die Irradiation autonomer Reflexe und ihre Beziehung zu gewissen pathologisch-physiologischen Erscheinungen. *Z. ges. Exper. Med.* 52, 499, 1926.
8. Schweizer, Alfred, Die Irradiation autonomer Reflexe. Karger, Basel, 1937, 215-217.
9. Bramwell, C. and King, J. T., *The Principles and Practice of Cardiology*. London, 1942, p. 198.
10. Colmers, R. A., Parasiernal Diaphragmatic Hernia with Report of a Case on the Right Side. *Radiology*, 37, 733, 1941.
11. Groedel, F. M., *Lehrbuch u. Atlas der Roentgendiagnostik*. Munchen, 1926, p. 667.
12. Akerlund, A., *Hernia diaphragmatica hiatus oesophagei vom anatomischen und roentgenologischen Gesichtspunkt*. *Aeta radiol.* 6, 3, 1926.
13. Harrington, S. W., Diagnosis and Treatment of various Types of Diaphragmatic Hernia. *Am. J. Surg.* 50/381, 1940.
14. Murphy, W. P. and Hay, W. E., Symptoms and Incidence of Anemia in Hernia at the Esophageal Hiatus. *Arch. Int. Med.* 72, 58, 1943.
15. Sahler, O. D. and Hampton, A. O., Bleeding in Hiatus Hernia. *Am. J. Roentgen.* 49, 433, 1943.
16. Reid, W. D., Hiatus Hernia simulating Cardiac Infarction. *New England J. Med.* 1940, 223, 50.
17. v. Bergmann, G., p. 70.
18. Wiggers, C. J., *Physiology in Health and Disease*, Phila., 1939, p. 294.
19. Groedel, F. M., The Differential Diagnosis between Abdominal Aneurysm and other Abdominal Diseases. *The Rev. Gastroenterol.* 1942, p. 219.
20. Osler, W., *The Principle and Practice of Medicine*. VI. Ed. Appleton, London and N. Y. p. 86.

3. All varieties of gastrointestinal diseases may lead to an erroneous diagnosis of heart disease due to the radiation of autonomous reflexes. Especially important amongst these are those suffering from reflex angina pectoris.

4. The patients with diaphragmatic hernia, mainly with hiatus herniae, must be mentioned as a separate



Figure 7—Case 17

group. In these cases the differential diagnosis is often extremely difficult.

5. Diseases of the circulatory system can often be masked by gastrointestinal symptoms.

The purpose of this paper is to show the manifold symptoms which may in one case mask a gastrointestinal disease and in another a circulatory disease. The few case reports demonstrate that close cooperation between the gastroenterologist and the cardiologist is absolutely essential.

The Nutritional Significance of Amino Acids and Proteins*

By

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ALTHOUGH the term protein (meaning first) was not used till 1839, when Mulder first applied it to designate the radical of a certain group of complex organic compounds, proteins have provided problems for investigation for centuries. The processing of cheese from milk and of ammonia from horn or from dung, the preparation of glue from connective tissue, the clarification of wines and of certain hot solutions by the use of egg white are examples.

In 1810 Wollaston made a very interesting discovery. He prepared cystine from a urinary calculus. This was the first instance of the isolation of an amino acid. In 1819, Proust obtained leucine through his study of cheese flavoring matter. In 1820, Braconnot was searching for a new source of sugar and recovered glycine by the acid hydrolysis of gelatin. The discovery of glycine was the first instance of the isolation of an amino acid by acid hydrolysis of a protein. In 1827, Plisson prepared aspartic acid. At the time when these amino acids were discovered, their relation to proteins had not been known. Progress was slow. Whereas Mulder's concept of protein structure was not accurate, nevertheless it created considerable interest among scientists of the 19th century, and such outstanding men as Liebig, Rithausen, Strecker, Schulze, Cramer, Drechsel, Kossel, Willstatter, Ehrlich, Hedin, Emil Fischer and many others, intensified their research on the chemistry of proteins and amino acids.

With the exception of tryptophane which is a product of the enzymatic hydrolysis of certain proteins and the two iodo-amino acids, diiodotyrosine, and thyroxine, which are obtained from alkaline hydrolysates of certain proteins, all the other amino acids are found in and can be isolated from the acid hydrolysates of proteins provided that they are present.

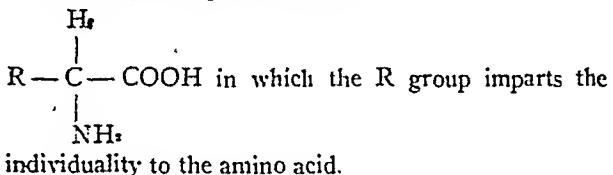
Proteins are built up from amino acids. The latter are linked together through the peptide bond to produce long peptide chains which usually consist of a large number of different amino acids.

Nutritionally, proteins occupy a unique position on account of their main constituent—amino acids. They form an essential component in our dietary requirements. We probably can dispense with carbohydrates and possibly with fats, but we must have proteins or their cleavage products, amino acids, in our diet.

Proteins are complex organic compounds. They are obtained from both animal and vegetable sources. They vary qualitatively and quantitatively in their amino acid content. For example, zein, the protein of corn, is deficient in lysine and in tryptophane; gliadin, the protein of wheat, lacks glycine and is low in its lysine content; gelatin is deficient in valine, methionine, trypto-

phane and low in cystine. In general, it may be said that most vegetable proteins are lacking in certain amino acids, whereas most animal proteins contain in varying amounts all indispensable amino acids. Unquestionably, from a dietary point of view, this is important. To insure the safety of our well being, different proteins need to be consumed, particularly those of vegetable origin and those of animal matters that lack certain essential amino acids. The purpose of this is to supply our body with its full requirements of the indispensable amino acids.

Amino acids are simple organic chemical compounds from which proteins are made. They occupy a unique position, in that they possess amphoteric properties. With the exception of proline and hydroxyproline which contain an amino group (NH_2), they all have one feature in common. They all contain at least one amino group (NH_2) and one carboxyl group. Their general formula may be represented as follows:



individuality to the amino acid.

Dispensability and Indispensability of Amino Acids

Proteins owe their nutritive significance to their constituents. On digestion, amino acids are liberated and pass unchanged into the portal circulation. They are then distributed throughout the system, utilized by the various tissues to form the many characteristic tissue proteins, or they are deaminated by the liver and the carbon-containing residue may then serve as a source of energy. One of the most astounding phenomena of life is the unerring accuracy with which a specific tissue cell builds up its specific tissue protein out of the mixture of amino acids that are constantly circulating in the blood.

Until recently, studies on the nutritive significance of individual amino acids was limited to animals. The high cost of pure amino acids was probably a deterring factor in not extending these investigations to man. In view of the invalid assumption on our part that, since amino acids are derived from proteins and in general our dietary protein intake is adequate, an understanding of the true status of amino acids would appear to be of academic interest only. But we are now beginning to understand the function of these simple compounds and especially their relation to hypoproteinemia. Our interest has been aroused. It has been found that hypoproteinemia is of frequent occurrence in man resulting from malnutrition and is often associated with many digestive and tropical diseases. Its occurrence in man probably explains the reasons for rapid onslaught of

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infectious diseases, slow healing of ulcers and wound ruptures, and poor recovery from major surgical operations, etc.

Nutritionally, the 22 naturally occurring amino acids, the chemical structure of which has been definitely established, are divided into two main classes (1) Dispensable and (2) Indispensable Amino Acids. An *Indispensable Amino Acid* may be defined as one that the body cannot synthesize, at least at a rate commensurate with its needs. A *Dispensable Amino Acid* is defined as one that the body can synthesize.

TABLE I

*Classification of the amino acids with respect to their growth effects**

<i>Dispensable</i>	<i>Indispensable</i>
Alanine	Histidine (1)
Aspartic Acid	Isoleucine
Cystine	Leucine
Cysteine	Lysine
Glutamic Acid	Methionine
Glycine (2)	Phenylalanine
Hydroxyproline	Threonine
Iodoarginic Acid	Tryptophane
Proline	Valine
Serine	Arginine (3)
Tyrosine	

(1) Histidine is indispensable to the rat but not to man.

(2) Glycine appears to be indispensable to the chick.

(3) Arginine can be synthesized by the animal organism but not at a rapid rate to meet the demands of normal growth.

The fact that the animal body can synthesize the dispensable amino acids does not necessarily mean that they are valueless in our dietary requirements. Little is known about the nutritional importance of these compounds since our efforts have been directed mainly to a study of the indispensable amino acids. Moreover, a dispensable amino acid to one species may be indispensable to another. (See Table I.) The recent investigation by Rose on histidine serves as an excellent illustration. This amino acid has been considered indispensable to the rat. Rose, however, found that the nitrogen balance of man could be maintained despite the absence of histidine from the diet. Almquist's investigation on glycine is also another example. He found this very simple amino acid to be essential to the dietary requirement of the chick. Moreover, there is the question of interconversion of amino acids. Phenylalanine is an indispensable amino acid and when fed to animals the animal organism can synthesize tyrosine from it. Hence a larger input of phenylalanine is required in the complete absence of tyrosine in the diet. Likewise is the story of methionine and cystine. Incorporation of the latter along with methionine in the diet enhances growth and reduces our requirement of methionine.

The recent work of Schoenheimer on isotopic amino acids has shed considerable light on our understanding of the metabolic functions and interconversion of amino acids in general. He introduced N^{15} into the molecules of a large number of amino acids and fed them to

animals. The results he obtained were most revealing. Thus when isotopic leucine was fed, it not only replaced a certain amount of the leucine that was present in the tissue proteins but it was transferred in particular to the carbon chains of the dicarboxylic, aspartic and glutamic acids. When isotopic tyrosine was fed the N^{15} was in part transferred to the α -amino group and not to the imidazole ring of histidine. Similarly when isotopic phenylalanine was fed isotopic tyrosine could be isolated. To the best of our knowledge, lysine is the only amino acid that does not accept N^{15} from any of the isotopic amino acids fed to animals.

DIETARY REQUIREMENTS, NITROGEN BALANCE AND THE INDISPENSABLE AMINO ACIDS

There had been considerable speculation as to the question of protein requirements in human beings. During the latter part of the 19th century Voit concluded that the daily consumption of 110-120 grams of protein was necessary. Owing to Voit's prestige in the field of nutrition this allowance of dietary protein remained unchallenged for almost half of a century. Recently, Sherman reinvestigated this subject and concluded that one gram of protein per kg. of body weight is acceptable for the adult. This standard has met with favor, and accordingly the Food and Nutrition Board of the National Research Council has recommended a diet containing 70 grams of protein for a man weighing 70 kg. and one containing 60 grams of protein for a woman weighing 56 kg. In this connection one must bear in mind that the dietary protein requirement per kg. of body weight is high in infancy, adolescence, in the pregnant and lactating woman, during the period of recovery from surgery, from severe burns and from certain diseases, and in malnutrition.

Nitrogen Balance

The estimation of nitrogen balance is considered an important factor in the determination of the dietary protein requirement. When the daily protein nitrogen intake exceeds the total nitrogen output a person is said to be in *positive nitrogen balance*, hence there is a storage of nitrogen as protein in the body. When the daily protein nitrogen in the diet is near or equals that of the daily nitrogen output, the body is said to be in *nitrogen equilibrium*, hence there is neither loss nor storage of protein in the body. On the other hand when the daily protein nitrogen intake is less than the daily nitrogen output, a person is said to be in *negative nitrogen balance*. This indicates a loss of body protein.

For a careful study of nitrogen balance an accurate knowledge of the total daily nitrogen intake must be determined. Briefly, the food must be analyzed for its nitrogen content and one must also determine the total nitrogen output. For this purpose a 24 hour collection of feces and urine must be made for the estimation of total nitrogen output. If extreme accuracy is desired, particularly during hot weather when there is considerable perspiration, during fever and exercise, etc., the nitrogen of the perspiration needs to be determined. For all intents and purposes, loss of nitrogen through the skin is usually omitted.

* See Rose, W. C., Physiol. Rev. 18, 109, 1938.

Whenever it is desirable to establish nitrogen balance the diet must be adjusted and an intimate knowledge is thereby gained relative to daily protein intake, number of calories, and ratio of protein to fat and carbohydrate. Should the amount of protein in the diet be increased, then the daily nitrogen output is also increased. On the other hand, if the daily protein intake is decreased, then the daily nitrogen output is also decreased.

During fasting, the rate of protein metabolism is greatly influenced by previous habit as to amounts of protein intake, and storage of carbohydrates and fats. This is illustrated in Falck's classical experiments. See Table II and III.

The results of von Noorden's clinical experiments on the adjustment of the diet from a high to a low protein intake are summarized in Table IV and those on the adjustment of the diet from a low to a high protein intake are presented in Table V.

TABLE II

The Effect of Fasting on Protein Metabolism of Falck's Lean Dog

Fasting Time Days	Protein Catabolized Grams per day
1-4	26.1
5-8	24.6
9-12	33.9
13-16	38.0
17-20	31.9
21-24	3.9

On the 25th day the dog died. It is interesting to note that on the 8th day there was a rise in nitrogen output, indicating that the dog used protein as a fuel.

TABLE III

The Effect of Fasting on Protein Metabolism of Falck's Fat Dog

Fasting Time Days	Protein Catabolized Grams per day
1-6	29.9
7-12	26.7
13-18	26.1
19-24	22.3
25-29	20.0
30-34	16.8
35-38	15.7
40-44	13.0
45-50	13.6
55-60	12.2

On the 21st day there was a sharp drop in nitrogen output and the animal died on the 25th day.

In contrast to the above experiment the data presented in Table III on the effect of fasting in protein metabolism of Falck's fat dog beautifully demonstrates that with plenty of available fuel as fat, the dog was able to adjust itself to a lower protein metabolism level and thus endure a 60 days fast.

Footnotes: Data found on Tables II, III, IV and V are taken from "Chemistry of Food and Nutrition", Chap. 10, 207. Through the courtesy of Dr. H. C. Sherman and The MacMillan Co., New York, 1933.

TABLE IV
Adjustment of Nitrogen Balance to a Lowered Protein Intake

Day	Nitrogen Intake gm.	Urinary Nitrogen Output gm.	Nitrogen Balance gm.
1	16.02	18.2	-2.18
2	16.02	17.0	-0.98
3	16.02	15.8	+0.22
4	16.02	16.0	+0.02
5	16.02	15.7	+0.32
Total nitrogen of food per day.....		16.96 gm.	
Average nitrogen in feces per day.....		0.94 gm.	
Absorbed nitrogen			16.02 gm.

TABLE V
Adjustment of Nitrogen Balance to an Increase in Protein Intake

NITROGEN					
Day	In Food gm.	In Feces gm.	Absorbed gm.	Catabolized gm.	Balance gm.
1	14.40	0.70	13.70	13.60	+0.10
2	14.40	0.70	13.70	13.80	-0.10
3	14.40	0.70	13.70	13.60	+0.10
4	20.96	0.82	20.14	16.80	+3.34
5	20.96	0.82	20.14	18.20	+1.94
6	20.96	0.82	20.14	19.50	+0.64
7	20.96	0.82	20.14	20.00	+0.14

RELATION OF INDISPENSABLE AMINO ACIDS TO NITROGEN BALANCE

The nutritive value of a protein depends on the presence of the indispensable amino acids among its constituents. See Table VI. A complete protein is considered as one that contains all of the essential amino acids listed in Table I. To achieve positive nitrogen balance in the rat Rose has demonstrated that all of the indispensable amino acids must be present. The omission of one from the ration causes the animal to be in negative nitrogen balance, hence loss of weight ensues. Recently, Rose extended his studies of amino acid requirements to man. He selected healthy young men to serve as the experimental subjects. Their diet consisted of purified amino acids, starch, sucrose, centrifugated butter, inorganic salts, and vitamins. At the start, the diet contained a mixture of the 10 amino acids previously found to be necessary to animals. The amino acid mixture furnished approximately 7 grams of nitrogen per day. Following the oral administration of this diet, the subjects came to nitrogen equilibrium within a few days and were maintained for a period of about 8 days. This investigation led Rose to conclude that the other amino acids noted to be dispensable to animals were also dispensable to man.

Subsequently single amino acids from the list of indispensables were omitted from the diet. When any one of the following amino acids: valine, leucine, isoleucine, lysine, methionine, tryptophane, phenylalanine and threonine was omitted from the diet, it was observed that the experimental subject was in negative nitrogen balance. Rose was considerably surprised when the omission of histidine from the diet of human beings did not cause a change in nitrogen equilibrium

in the experimental human subject. Thus it was obvious that histidine was not indispensable to man.

SIGNIFICANCE OF THE OMISSION OF INDISPENSABLE AMINO ACIDS FROM THE DIET

The literature on this subject covers in general the results obtained on animal experimentation. In general it may be stated that the omission of any of the indispensable amino acids from the diet of animals results in a negative nitrogen balance, loss of appetite, loss of weight, alopecia, nervousness and death.

Tryptophane

Since the discovery of this amino acid by Hopkins and Cole, the indispensability of tryptophane has been well established in animals and more recently in man. Recently it was observed by several investigators that the continued omission of tryptophane from the diet

a mixture obtained by the use of acid hydrolyzed casein, it was observed that both forms are equally satisfactory for the purpose of growth. Du Vigneaud and co-workers studied the action of *d*- and *l*-tryptophane and reported that the two isomers are equally effective in promoting growth. This was confirmed by Berg.

Valine. According to Rose and Epstein, young growing rats placed on a diet deficient in valine not only exhibited the usual syndrome of the amino acid deficiency but became extremely sensitive to touch and manifested a lack of co-ordination in movement. The addition of valine to the diet restored these animals to a normal condition.

Lysine. Recently, Harris, Neuberger, and Sanger have published a detailed report on the pathology of rats fed a diet deficient in lysine. They observed cessation of growth and hypoproteinemia due to a general inhibition of protein synthesis. These manifestations

TABLE VI

Indispensable Amino Acids Content of Certain Tissue Proteins

Protein	Total N	Percent	Aarginine Percent	Histidine Percent	Isoleucine Percent	Leucine Percent	Lysine Percent	Methionine Percent	Phenylalanine Percent	Threonine Percent	Tryptophane Percent	Valine Percent
	Percent	Percent	Percent	Percent	Percent	Percent	Percent	Percent	Percent	Percent	Percent	Percent
Brain	14.1	6.5	2.1	3.5	11.0	6.4	2—	5.2	5.2	0.7	0.7	4.3
Serum	14.9	5.9	2.3	3.2	14.8	7.8	3	7.1	5.7	0.4	0.4	6.7
Serum Albumin	15.7	6.2	2.8	2.0	16.7	8.5	4	7.8	5.6	0.3	0.3	4.1
Serum Globulin	14.9	4.3	1.8	5.1	—	5.8	2	5.9	6.0	0.7	0.7	—
Casein	14.7	5.3	1.9	4.2	14.8	5.9	3	5.8	4.6	1.2	1.2	5.2
Lactalbumin	13.6	3.0	1.4	5.1	17.2	5.9	3—	4.8	4.5	2.0	2.0	4.0
Egg Albumin	13.9	5.6	1.5	5.0	13.6	5.0	5	6.8	3.6	1.4	1.4	4.5
Egg Yolk	14.6	7.7	2.3	—	—	5.0	3	4.0	4.4	1.5	1.5	—
Muscle	16.1	7.7	1.7	3.0	11.0	6.9	3.1*	4.9	3.5	0.6	0.6	3.6
Heart	14.8	6.8	2.3	4.0	13.4	7.9	3.4*	5.3	3.7	0.7	0.7	3.2
Tripe	15.3	8.9	1.7	3.0	10.6	6.5	2.7*	4.8	3.3	0.4	0.4	3.0
Liver	13.3	6.0	2.0	3.5	11.6	4.6	2.9*	6.2	4.6	1.0	1.0	3.6
Kidney	15.6	6.5	1.8	3.5	13.2	5.6	2.8*	5.5	4.4	0.6	0.6	3.8
Lung	15.3	7.3	2.3	2.8	11.5	4.6	2.5*	5.5	3.6	0.3	0.3	3.4
Spleen	15.7	7.2	1.8	3.4	11.9	6.8	4.5	3.7	0.6	0.6	0.6	4.7
Pancreas	15.5	6.8	2.5	3.3	9.3	5.5	4.3	4.0	0.5	0.5	0.5	4.1

* The major portion of the data found in this table are taken from Blok, R. J. and Bolling, D. "The Determination of the Amino Acids" Those figures marked with asterisks are taken from: Bech, E. F., Munks, B., and Robinson, A., J. Biol. Chem. 148, 431, 1943.

of the rat caused the development of cataract in about 8 weeks, followed by loss of sight. During the early stages of tryptophane deficiency, nitrogen balance can be restored to the experimental animal, but once lesions such as cataract have developed, the incorporation of tryptophane in the diet will not cause the recovery of sight in the experimental animal. In other words, irreversible pathologic changes have taken place.

Man's daily requirement of tryptophane is not definitely established. On the basis of the average tryptophane content of foods, a person daily consumes from 0.5 gram to one gram. Tryptophane is one of the four amino acids that can be utilized by the body in either of its optical isomers. According to Berg and Potgeiter who studied the utilization of *l*- and *dl*-tryptophane in

in animals are not specific to a lysine deficiency but are characteristic of any animal that is not receiving a complete mixture of the essential amino acids. However, lysine is unique in one respect. It was pointed out earlier in this discussion that by the use of isotopic nitrogen this amino acid will not enter into the exchange reactions as is the case of other amino acids. Thus it appears that for normal growth, the total requirement of lysine must be incorporated in the diet. Once this amino acid is deaminated it loses its usual nutritional significance.

Phenylalanine. On a diet deficient in this amino acid, rats develop the usual symptoms. They can be cured by restoring this compound to their ration. Phenylalanine can replace tyrosine in the diet but the latter cannot replace the former. It is significant to note that in the animal body this indispensable amino acid is not only the precursor of tyrosine but probably also of such im-

Footnote: While this paper was in progress Albanese, Holt, Frankston and Irby reported that human subjects kept on a histidine-deficient diet remained in nitrogen equilibrium but lost weight. (Bull. Johns Hopkins Hosp. 74, 251, 1944).

portant hormones as thyroxine and epinephrine. The animal body can utilize both of its optical isomers.

Methionine. Aside from its indispensability in the diet, this amino acid plays an important role in nutrition. Because of the presence of a labile methyl group in its chemical structure, methionine is the precursor of the methyl group of choline and therefore exhibits a lipotropic effect. On a diet low in methionine an animal can actually show an overall gain in weight due to fatty infiltration of the liver. Obviously this is the result of the restriction of the intake of methylating agencies rather than the lack of methionine *per se*.

This amino acid is also important on account of its sulfur content. Adequate amounts of it in the diet permit the animal body to synthesize cystine, otherwise the diet must be enriched with the latter amino acid. The animal body can utilize both of the optical isomers of methionine.

Isoleucine, Leucine and Threonine. The removal from the diet of any of these three amino acids results in loss of weight, loss of appetite, alopecia, and nervousness. These symptoms can be corrected by returning the missing amino acid to the diet.

Histidine. This amino acid was found essential to animals. Its omission from the diet of the rat causes the usual symptoms. According to Rose, histidine is not essential to man inasmuch as nitrogen balance is concerned. Its omission from the diet of human beings for a long period of time has not been investigated.

Arginine. Whereas the animal body can synthesize this amino acid, its incorporation in the diet of rats enhances growth. There are reports in the literature that a lack of this compound results in a decreased spermatogenesis. This needs confirmation since several generations of rats have been raised without arginine in the diet. When the animal is growing it may not be able to synthesize this amino acid sufficiently fast to meet its dietary requirements.

TABLE VII

Estimation of Daily Consumption of Indispensable Amino Acids (including Cystine and Arginine) Occurring in Diets Containing Varying Amounts of Proteins:

Amino Acids	Amounts of Amino Acids			
	A-80 gm.	A-60 gm.	B-89 gm.	B-60 gm.
Cystine	0.94	0.71	1.22	0.82
Methionine	2.35	1.76	2.82	1.90
Arginine	4.26	3.21	4.75	3.20
Histidine	1.41	1.06	1.81	1.22
Lysine	4.16	3.12	5.09	3.43
Tryptophane	0.83	0.62	1.06	0.72
Phenylalanine	3.78	2.84	4.29	2.89
Threonine	2.87	2.15	3.41	2.30
Leucine	8.65	6.49	10.70	7.20
Valine	2.83	2.12	4.21	2.84
Isoleucine	2.77	2.08	3.28	2.20

Figures found in columns A-80 and B-89 are taken from Block, R. J., Yale J. Biol. Med. 15, 723, 1943.

Figures given in column A-60 are obtained by multiplying those in A-80 by the factor 60/80 and those in B-60 by multiplying values given in B-89 by the factor 60/89.

TABLE VIII
Daily Requirements of Pure Amino Acids for Maintenance of Nitrogen Balance for a Man Weighing 60 Kg.

Amino Acids	Amount gm.
<i>I</i> (+)-Arginine hydrochloride	5.2
<i>I</i> (+)-Histidine hydrochloride	2.6
<i>d</i> 1 —Lysine hydrochloride	8.0
<i>I</i> (-)-Leucine	10.0
<i>d</i> 1 —Isoleucine	7.0
<i>d</i> 1 —Valine	9.0
<i>d</i> 1 —Methionine	4.0
<i>d</i> 1 —Threonine	7.0
<i>d</i> 1 —Phenylalanine	4.5
<i>d</i> 1 —Tryptophane	1.2
Glycine	6.5

The above data have been reported by S. Madden in the Proceedings of the Institute of Medicine of Chicago, 15, 25-27, 1944.

Madden stated that similar mixtures of amino acids, as indicated in the above table, given parenterally to supply 85% of the total nitrogen intake with the remaining nitrogen being contained in the oral diet of carbohydrates, fats and accessory factors, have produced nitrogen balance and sustained weight gain in man for periods as long as 75 consecutive days.

PARENTERAL ADMINISTRATION OF AMINO ACIDS

The importance of amino acids in the diets of man and of animals has been discussed. The nutritive significance of these compounds cannot be questioned. Every living cell in our system contains protein in its protoplasmic structure and requires amino acids to synthesize its characteristic protein. Countless number of cells are destroyed daily. These have to be replaced. In malnutrition, in cases of improper nitrogen utilization, and in others when hypoproteinemia has developed, the body has been in negative nitrogen balance—there has been a greater loss of nitrogen than can be accounted for by nitrogen intake.

Amino acids do not seem to be stored in the body in the sense that carbohydrates and fats are. They are used up as fast as they are circulated in the blood stream to replace the tear and wear of tissue proteins or catabolized to yield energy.

Recently there has been considerable interest shown in amino acid therapy. This interest is gaining momentum. It is therefore essential to have a clear understanding of the fundamentals of protein intake and the fate of their constituents, the amino acids. A bird's-eye view of the literature has been presented. For a number of years, in pre- and post-operative conditions, man's caloric requirement has been partially met by intravenous administration of sterile dextrose solutions. This has unquestionably served a useful purpose. However, man cannot synthesize tissue proteins from carbohydrates or from fat. It becomes therefore obvious that in order to prevent patients under such conditions from incurring a nitrogen debt, proteins or their equivalent amino acids must be given. Parenteral injections of most proteins other than whole blood or blood plasma cannot be given. However, it is both safe and feasible to administer amino acids parenterally.

Following the intravenous injections of sterile solutions of amino acids into man with and without dextrose, numerous investigators noted that nitrogen balance can be obtained, while others observed protein regeneration, better healing of wounds, quicker recovery from major surgical operations, healing of burns, and of ulcers, and, in general, a better feeling of well being.

For parenteral administration a suitable mixture must contain all the indispensable amino acids. This is obvious since the object is to achieve nitrogen equilibrium and preferably positive nitrogen balance. The quantitative requirement of man is not fully known but one can well estimate his needs from his nitrogen output. Thus, if the latter has been found to be 10 grams nitrogen per day, a minimum of 10 grams nitrogen as amino acids is required for maintenance of nitrogen equilibrium. To produce positive nitrogen balance a larger quantity is required.

To obtain the maximum benefit of amino acids administered for the maintenance of nitrogen balance and tissue repair, it is mandatory to (1) give sufficient amounts of carbohydrates along with the amino acids and (2) supply the body with its daily vitamin requirements. Obviously, the amount of glucose that needs to be given depends on the age, weight and condition of the individual. For a patient at rest, a mini-

mum of 1200 to 1600 total calories may be required per day. The glucose administered furnishes the needed calories, thus sparing the amino acids for the purpose of meeting the nitrogen requirements. Considerable clinical research is necessary to determine the optimal ratio of carbohydrates to amino acids.

Since purified amino acids are not available in quantities and at reasonable cost for clinical use, it is equally satisfactory to use a suitable hydrolysate of a complete protein. This has been tried and tested clinically. In this connection it is desirable to point out that it is of paramount importance that the solution be sterile, pyrogen free and non-allergenic. It must consist of amino acids only and it must not contain semi-digested proteins and unknown harmful substances that may be derived from agents used for the partial breakdown of proteins. It is thus considerably safer to use an acid hydrolysate of a protein such as casein, particularly since the catalytic agent is not only capable of completely hydrolyzing the protein to simple amino acids but it also can be quantitatively removed from the resulting mixture of amino acids.

Since acid hydrolysis destroys tryptophane, to render this mixture complete, this amino acid must be replaced in amounts sufficient to achieve nitrogen balance in man.

Arterial Thrombosis Associated With Chronic Ulcerative Colitis*

By

MARY E. MARTIN, M.D.*

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THROMBOSIS of blood vessels with chronic ulcerative colitis is rare. The only report of progressive thrombosis of large arteries is by Bargen and Barker in 1936. (1) They observed thrombosis or thrombo-phlebitis sufficiently extensive to be a clinical problem in only 18 of 1500 patients with chronic ulcerative colitis. Less serious thrombosis of smaller vessels, chiefly veins, was more frequent. In the patient with thrombosis of the aorta and its larger branches recorded by Bargen and Barker both iliac and femoral veins, the left renal vein, and the vena cava had thrombi. They discussed the conditions of this patient and the thrombosis and thrombophlebitis of smaller vessels in other patients and associated these changes with the extensive disease of the colon and accompanying peritonitis; toxemia, profound anemia, and venous stasis. The conditions disclosed by postmortem examination of the patient of my report had additional features which seemed related to the development of the arterial thrombosis.

A white female, aged 56 years, entered St. Luke's Hospital in the care of Dr. De Bere on October 2, 1943. Death occurred on October 8, 1943. She had a

hemorrhoidectomy in January 1941. Excepting bright red blood in the stool there had been no unusual symptoms. Physical examination at that time disclosed nothing unusual. She was readmitted to St. Luke's Hospital in December of 1941 and after five days was discharged with the diagnosis of chronic ulcerative colitis. She had had a profuse bloody diarrhea and abdominal cramps for three weeks and for two weeks emesis and intolerance of food. Within three weeks before admission she had lost 25 pounds weight. The blood pressure was 158/78, the temperature 99.4 degrees, the pulse 88 and the respiratory rate 22 per minute. The patient was acutely ill. The x-ray examination was reported as showing serration of the colon particularly throughout the transverse and descending portions. The Kahn test of the blood was negative. The erythrocyte count was 3,750,000 per cu. mm. and there were 9.9 grams of hemoglobin. The leucocyte count was 13,050 per cu. mm. There was a marked achromia. Differential counts of the leucocytes were not unusual. The stools were liquid, frequent, and consistently contained occult and usually gross blood. Examinations for parasitic trophozoites and cysts were negative as were cultures for paratyphoid, typhoid, and dysentery bacteria. The Widal was negative. There was temporary improve-

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ment on non-specific supportive and dietary therapy. The temperature during this short hospital stay rose daily to about 100 degrees F. and was accompanied by a corresponding elevation of the pulse rate. She was discharged after five days.

The final admission was on October 2, 1943, eighteen months later. During the interim the profuse diarrhea, steady weight loss, and progressive anemia had persisted with slight temporary remissions. Shortly before admission she had a sudden excruciating pain and

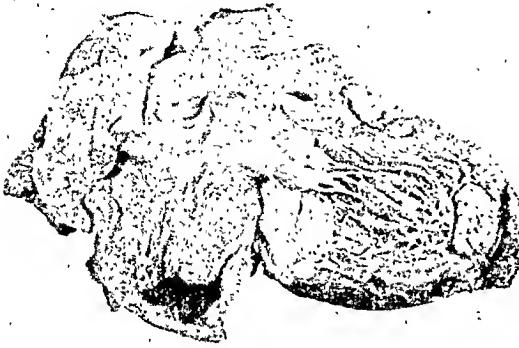


Figure 1—Photograph of the heart showing the mural thrombus at the apex of the left ventricle.

numbness in both lower extremities extending to the groin on the right side and to the midcalf on the left. The skin of these regions was cold and shortly became cyanotic. Arterial pulsation was absent below the groin of the right leg and below the knee of the left leg. Trophic changes of the skin of the toes and feet progressed rapidly. The patient became irrational, uncooperative and incoherent. Fecal and urinary incontinence developed. The temperature on admission was normal but fluctuated widely thereafter, reaching 102° F. on the fourth hospital day. She grew worse steadily and died on the sixth day in the hospital.

The postmortem examination was performed about four hours after death by Edwin F. Hirsch. The skin changes observed externally included bluish-purple discoloration of the skin of both thighs, legs, and feet. There was black discoloration of the entire distal phalanx of the right great toe and the tips of the other toes of the right foot. The skin tissue here was dry. The skin was superficially denuded over large regions on the surfaces of the lower extremities below the knee.

The peritoneum was smooth and glistening. There were petechial hemorrhages and foci of fat necrosis in the pancreatic fat tissues. Beneath the capsule of each kidney were small hemorrhages, in addition to large lesions to be mentioned presently. The heart weighed 350 grams. There were no unusual changes of the valve structures. The lining of the coronary arteries had slight fatty changes but their lumens were widely patent. The myocardium of the left ventricle and of the septum on broad surfaces made by cutting was red-brown, firm, had multiple small foci of grey and yellow, and at one place near the apex a fibrous scar 1 cm. in diameter.

The thickness of the myocardium of the lateral wall at the level of the mitral ring was 1.8 cms. but toward the apex it was reduced to a thickness of 0.5 cms. and here extending onto the septum was a red-grey firm mural thrombus of the endocardium firmly attached to the lining near the apex, 3 by 2.5 and about 2 cms. thick. (Fig. I) The lining of the superior and inferior cavae and of the left and right common iliac and left and right renal veins was smooth. The wall of the aorta was about 2 mms. thick. The lining of the thoracic portion had fatty changes and in the abdominal portion these were more marked. In the lumen beginning at the diaphragm and loosely adherent was a grey-red thrombus. (Fig. II) It extended downward 5.5 cms., was 2 cms. wide and 5 to 8 mms. thick. Below this was a loose mass of grey-red firm blood clot material about one-half as long. In the lumen of the left common iliac artery was a grey-red thrombus which extended to within 1 cm. of the bifurcation of the vessel. Similar thrombus material occluded the lumen of the right common iliac artery and extended almost to the bifurcation. In the left renal artery beginning 2.5 cms. from its ostium was a firm grey-red thrombus reducing the channel markedly. The lower edge of the thrombus of the aorta was 5 mms. above the upper margin of the ostium of the left renal artery. The thrombus in the left renal artery extended to within 2 mms. of the kidney. (Fig. III) At the upper and lower poles of the kidney were wedge-shaped, dark red and slightly depressed infarcts, the lower 2 by 2 cms. and the upper slightly larger. Examination of the brain disclosed nothing unusual.



Figure 2—Photograph of the thoracic aorta (right) and abdominal aorta (left). Thrombus remains in the lumen of the aorta, the left renal artery and in the common iliac arteries.

There were marked changes in the lining of the large bowel and rectum. (Fig. IV and V) Beginning sharply at the ileocecal valve and extending to the anal ring the mucosa was extensively ulcerated. These changes involved the cecum and descending colon most extensively but were present throughout. There were papillary elevations and polypoid red-brown folds with overhanging edges. They occasionally formed bridges, ranged to 2 by 1 cms., and elevated to 0.8 cms. These were most numerous in the descending colon. The mu-

cosa adjacent to the elevations and beneath the bridges was ulcerated or finely puckered, and the wall of the bowel was thickened. The mucosa of the rectum was involved in the inflammatory and indurative process and there was an ano-rectal fistula. Material from the ulcerated regions was examined by direct warm-stage method and in iodine stained preparations but no trophozoites or cysts were present.

The chief items of the anatomical diagnosis were:
 Extensive chronic ulcerative colitis and proctitis;
 Subacute mural thrombotic endocarditis of the left ventricle;
 Focal fibroplastic myocarditis, (embolic);
 Infarcts of the kidneys and pancreatic fat tissues;
 Obdurator thrombosis of the aorta, of the right and left renal artery;
 Recent infarcts of the left kidney.

Cultural examinations of the mural thrombus of the endocardium for bacteria were unsatisfactory because the mediums were overgrown by *B. proteus*. Cultures of the heart blood, the pericardial fluid and spinal fluid had no growth in 72 hrs.

Histological examinations of tissues of the colon disclosed that the mucosa was absent over large regions. Here exudates covered a surface of chronic granulation tissues. The exudate cells were mainly lymphocytes and plasma cells with moderate numbers of polynuclear leucocytes, many of them eosinophilic. The adjacent mucosa was in polyp-like folds overhanging the ulcerated regions. The submucosa was widely infiltrated by

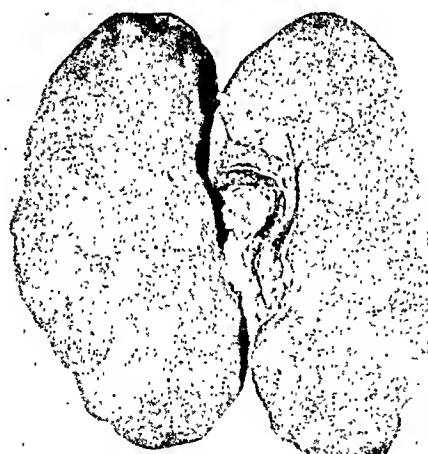


Figure 3—Photograph of the left kidney. The thrombus remains in the lumen of the renal artery. The dark regions of the infarction are at the upper and lower poles.

the exudate cells. In some places beneath the ulcerated regions exudates extended between bundles of slightly hypertrophied muscle into the subserosal tissues. In preparations stained with iron hematoxylin no trophozoites or cysts were identified.

Twenty-four sections of the myocardium cut from different levels of three blocks were examined. Multiple

regions of infarction, small but not uniform in size, were found in all the sections examined. As judged by the cellularity of the tissue, the presence of reactive cells, and the amount of fibrous tissue replacement these lesions varied in age. A few were cellular, edematous, and with slight infiltrations of lymphocytes and plasma cells and an occasional polynuclear leucocyte. Others were fibroplastic tissue with few or no exudate cells. Some were dense fibrous or acellular hyaline tissue. In the dense fibrous tissues in a few places were macro-

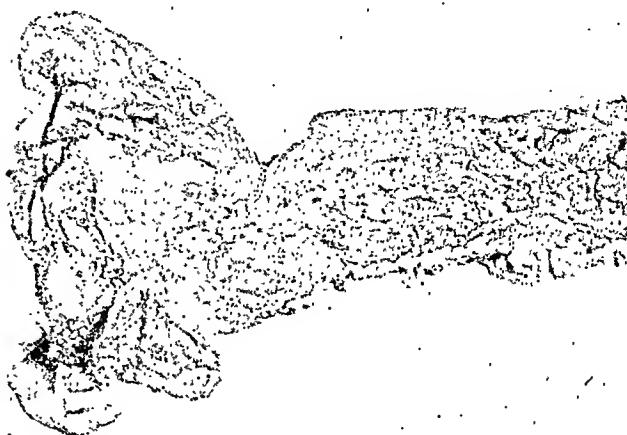


Figure 4—Photograph of the cecum and first portion of the ascending colon.

phages with brown granular pigment. The smaller branches of the coronary arteries were without marked thickening of their walls. They had widely patent lumens. In sections cut from various levels and stained with Giemsa stain and with Methylene blue no bacteria were seen. Many sections were cut also at different levels from tissues of the myocardium and endocardium in the region of the mural thrombus. In the deeper portions of these tissues were focal lesions like those elsewhere in the myocardium. Under the thrombus the endocardium was thickened by edematous fibrous tissue. In the endocardium there was a slight infiltration of lymphocytes, plasma cells, and a few polynuclear leucocytes. The thrombus was composed of masses of blood cell elements and fibrin, superficially laminated. In the deeper portions at a few levels was slight organization. No bacteria were demonstrated in these sections.

Evidence of embolism was found also in the spleen where many small focal masses of cellular tissue interpreted as reactive were scattered throughout the pulp. There were also recent hemorrhages. In addition to the large regions of infarction in the left kidney multiple small regions of hemorrhage and a few focal fibrous scars were present.

Sections from the aorta in the region of the loosely adherent thrombus had the changes of atherosclerosis. There was no organization of the thrombus and no cellular reaction in the tissues beneath. Tissues from the left common iliac artery included thrombus material in the lumen. In the intima and subintimal tissues were small recent extravasations of red cells and a few leucocytes. The cellular reaction was limited to the super-

ficial portions and, though more definite than at the higher level, was slight.

In this progressive arterial thrombosis complicating chronic ulcerative colitis venous stasis, profound anemia, toxemia, and extensive ulcerative disease of the colon were present. However, there was no evidence of peritonitis and the arterial thrombosis was unaccompanied by thrombophlebitis or venous thrombosis. The history

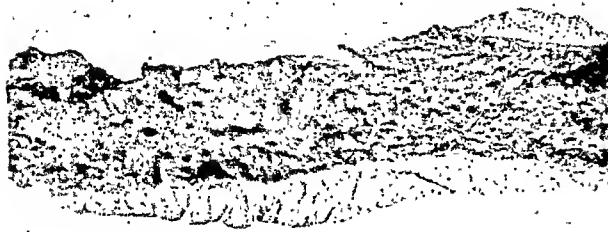


Figure 5—Photograph of the descending colon.

mural thrombus of the parietal endocardium of the left ventricle suggests that this was the origin of the thrombus. Thrombotic parietal endocarditis has been indicates a sudden vascular accident in the lower

extremities, and the postmortem demonstration of a described in chronic debilitating disease and is considered by Gross and Freedberg (2) to occur in 85 percent of the cases on the basis of previous damage. Sudden closure of the peripheral vessels even with the possibility of embolism may be thrombotic according to Gosset, Bertrand, and Patel (3). The minimal reaction in the wall of the iliac artery and the absence of reaction in the tissues in the wall of the aorta of this patient is considered significant. The presence of fibrous scars and the described endocarditis beneath the parietal thrombus of the left ventricle indicates its greater age.

Embolii, mainly small, have been reported by Bargen and Barker in 14 of 43 patients with chronic ulcerative colitis and examined postmortem. These were mainly in the kidneys, spleen, and lung. The lesions found in the myocardium of this patient as well as those of the spleen, kidneys, and pancreatic fat tissues are considered embolic, complicating the extensive ulcerative colitis.

SUMMARY

Extensive thrombosis of the abdominal aorta, the right and left common iliac arteries and the left renal arteries occurred in a patient with chronic ulcerative colitis.

Embolii from a mural thrombotic endocarditis of the left ventricle are considered the cause of the arterial occlusions.

Small older infarcts of the kidneys, spleen, pancreatic tissues and myocardium were also present, and interpreted as related to a septicemia, the source of infection being the deeply ulcerated colon.

REFERENCES

1. Bargen, J. A., and Barker, D. W.: Extensive arterial and venous thrombosis complicating chronic ulcerative colitis. *Arch. of Int. Med.*, Vol. 58, pp. 17-31, 1936.
2. Gross, L., and Freedberg, C. F.: Nonbacterial thrombotic endocarditis. *Arch. Int. Med.*, Vol. 58, pp. 620-640, 1936.
3. Gosset, A., Bertrand, I., and Patel Jean: Sur la physio-pathologie des embolies arterielles des membres (recherches experimentales). *Ann. l'anat. Path.*, Vol. 9, pp. 841-862, 1932.
4. Willius, F. A.: Mode of death in various types of heart disease. *Amer. J. M. Sc.*, Vol. 171, pp. 480-485, 1926.

Book Reviews

Patients Have Families. By Henry B. Richardson, M.D. Pp. 405, (\$3.00), New York, The Commonwealth Fund, 1945.

By turning medicine sidewise, in order to view it from the family angle, by adding copious infusions of psychosomatic philosophy and psychoanalysis and stirring the pudding with economic flavoring, there is obtained ostensibly a new science which in reality remains the old science in spite of the innovations. The author has completed a study which nevertheless deserves consideration because many of the platitudes he writes are those which need emphasis. The book is eminently well organized and beautifully written and published. The author feels that the time is ripe for a coordinated attack on the problems of family adjustment in relation to the maintenance of health and the

treatment of illness. Here are revealing details about the family "equilibrium" both from a psychological and an economic angle with appended case histories. The book should prove of real value to those who are interested in "social work". Physicians will enjoy it, provided they can adopt the author's sincerity.

The author abhors the "dichotomy" of mind-body, and asks us to view the patient as a whole individual in whom soma and psyche are merely two seemingly different aspects of the one reality. While this emphasis on "whole-ism" is increasing in psychosomatic studies, most doctors of medicine still justifiably regard the mind and body as really different. They must remain different until our profound human ignorance is very deeply altered. It will require more than a novel departmentalization of medicine to retire a mode of

thinking ingrained in us from time immemorial. Let us admit that mind and body are different, though coming together palpably in emotional reactions. Let us fish patiently in the waters of pluralism for such small fry as we may obtain, rather than strain ourselves harpooning an alleged monistic organism which flounders in the depths of the sea.

Every astute practitioner,—and the woods are full of them,—realizes the importance of the patient as a human person, as well as a pathologic exhibit. He is becoming bored by being too frequently reminded of the importance of emotional attitudes, some of which are instigated and perpetuated by one or more members of his family. Some time ago I tired of the "family" novel and longed for one dealing utterly with an orphan. We all know that family frictions are an eternal fixture in human society. Every man has suffered as well as profited from his own family connections. Do we need to make a new department of medicine out of the family? We could also write a book on the influence of business on the patient and label it "Patients have Business Associates". We might compose another on the influence of the nation on individuals and call it "Patients have National Affiliations", in which many causes for neurosis could be listed, from income taxes and boondoggling down to the irritating influence which some socialistic trends exert especially on doctors.

These new departmentalizations of medicine merely intensify what the practitioner long has done by himself. None but the hospital type of internist or psychiatrist ever wandered far from the home-setting of the patient. Only adventurers in laboratories or clinics ever conceived of a patient as a piece of meat, or, psychically, as an uncaused phenomenon. It was only when such investigators left their institutions that they made the startling discovery that patients have families and are influenced by them. But to make the family a frame

of reference for the science of medicine seems to the reviewer an unjustifiable effort and one which has the aroma of socialism, rather than of medicine.

The book, with its popular title, may prove interesting reading to the public, especially the "social workers" and "case experts" and even to physicians who possess a taste for innovation. Physicians never will become social workers or technical psychiatrists but will remain merely doctors, who, in the brief span of their professional careers, will spend most of their time diagnosing diseases, and very little time contemplating the dichotomy of soma and psyché. Philosophy may include the individual, the group, or both. Socialism, taking the group, must hide the individual. Medicine must take the individual, body, mind and soul, just as he is, not merely as a reflex of his group, but as something also in his own right.

The Chemistry and Pharmacy of Vegetable Drugs.
By Noel L. Allport, Pp. 252, (\$4.50), Brooklyn, N. Y.,
The Chemical Publishing Co., Inc.

Here is a well illustrated review of vegetable drugs, including the important alkaloids, diuretics, carminatives, rubefacients, expectorants, anti-helminthics and flavoring and coloring agents. Methods of preparation, tests for purity, various forms for administration and interesting descriptions of the sources and commercial states are given in almost each instance. The author points out that the use of vegetable drugs probably never will be discontinued, and cites penicillin as an unexpected "find" from the vegetable kingdom, from which others may be expected to emerge. While it is true that hormones and vitamins have accomplished good results, we are properly reminded that a good prescriber can still obtain excellent effects from the use of a wide range of vegetable drugs. The book is stimulating and up-to-the minute.

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MOUTH AND ESOPHAGUS

HAIGHT, C.: *Congenital atresia of the esophagus with tracheo-esophageal fistula.* (*Ann. Surg.*, v. 120, p. 623, Oct., 1944)

In congenital atresia of the esophagus the upper end of the esophagus ends as a blind pouch in nearly all cases. The upper end of the lower segment usually forms a tracheo-esophageal fistula. The condition is, of course, incompatible with life. Attacks of choking dyspnea and cyanosis on attempting to swallow fluid leads to the suspicion of congenital obstructions. Fluoroscopic observation of swallowing of iodized oil confirms the suspicion. Tracheo-esophageal fistula also is shown by the presence of air in the stomach.

Haight had a series of 32 patients with congenital atresia. All 32 cases showed a blind pouch in the upper segment. The upper segment was between 1.2 and 1.5 centimeters in diameter. The gap between the two segments varied between 1.5 and 3 centimeters. Twenty nine of the 32 patients had a tracheo-esophageal fistula and air was noted in the stomach or intestine in 26 of them. Exploratory operations were performed in 24 patients and reconstruction of the esophagus attempted in 16. Six of these 16 are still living from 7 months to three years and one month after operation.

Surgery involved correction of the esophageal obstruction so that aspiration pneumonia would not occur, closure of the tracheo-esophageal fistula and provision of some means for feeding the infant. The indirect surgical approach is a three-stage operation involving extrapleural ligation of the fistula, exteriorization of the upper esophageal segment and gastrostomy. However, the ideal surgical principle in correction of the anomaly is a direct one-stage reconstruction of the esophageal segments. Haight discusses the merits and contraindications for the operation and presents the operative procedures in detail. Factors to be observed in the pre- and post-operative treatment of the patient are discussed.—I. M. Theone.

BUSCHKE, F. AND CANTRIL, S.: *Supervoltage therapy of esophageal carcinoma.* (*Radiology*, v. 42, p. 480, 1944).

The results of therapy of thoracic esophageal tumors are analyzed with the conclusion that 200 kv. therapy is only palliative. Curative measures must be found in some other form of treatment. Five cases in 4½ years were treated with 800 kv. with encouraging re-

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suits. Greater depth can be attained with 800 than with 200 kv., also the higher voltage is better received by the patient, and the end results may be found to be better. Metastasis is a contraindication.—N. M. Small.

TRUEBLOOD, D. V.: *Clinical observations and surgical experiences with parotid tumors.* (*Western J. Surg.*, v. 52, p. 109, 1944.)

In cases of parotid tumors, it is insufficient to only remove the mass from within the gland. Enucleation does not achieve the results desired because the tumor tends to recur. The operation of choice is the removal of the entire parotid gland with care taken to save the facial nerve. Nine cases are reported.—F. X. Chockley.

BOWEL

RENDICH, R. A. AND HARRINGTON, J. A.: *Roentgenologic observations in mesenteric thrombosis.* (*Am. J. Roentgenol. Rad. Therap.*, v. 52, p. 317, Sept. 1944.)

In three cases of superior mesenteric thrombosis the authors found one roentgenologic feature which was common and which they believe may be of some value as a diagnostic aid. The small bowel and the right half of the colon were distended and presented the distinct picture of mechanical obstruction. Gas in the bowel ended abruptly at the left end of the transverse colon; the distended segments were those supplied by the thrombosed superior mesenteric vessels. A barium enema can pass thru the distended portion so that this may constitute a method of distinguishing between the similar roentgenologic appearance of mesenteric occlusion and true intestinal obstruction. One of the three patients died, the other two recovered after resection of the involved bowel.—N. M. Small.

BAUMHAUER, J. H.: *Treatment of chronic intestinal indigestion with vitamin B complex and liver extract.* (*Alabama State Med. Assoc. J.*, v. 14, p. 66, Sept., 1944.)

Celiac disease is a form of chronic intestinal indigestion affecting infants and is believed to be due to faulty intestinal absorption. Children with chronic intestinal indigestion show poor appetite, do not gain weight, have diarrhea, are susceptible to respiratory infections, show aversion to normal play and exhibit fretfulness, irritability and fatigue. Restless sleep, grinding of teeth and night terrors are common. The child may

develop tetany or convulsions.

The patients included in this report received weekly separate injections of vitamin B complex and liver extract. In addition to the parenteral therapy vitamin B complex, other vitamins and liver extract were given by mouth. The diet was liberal. Iron was given in cases of iron anemia. Failure to respond was found when the child had some infection, either acute or chronic. In the absence of infection, favorable results were obtained. The child became more active, less irritable or fretful, gained weight and showed general increase in well-being.—G. Klenner.

Woods, F. M. AND HANLON, C. R.: *Inflammatory stricture of the rectum: an analysis of one hundred and ninety-two cases, including thirty-five treated by rectosigmoid resection.* (*Ann. Surg.*, v. 120, p. 598, Oct., 1944.)

The causal relationship of lymphopathia venereum to rectal stricture is recognized but there still is no treatment which is regarded by all as being satisfactory. Probably variations in the extent of the stricture, complications due to ulcerations, fistulas, etc., and the degree of the patient's cooperation are factors for the divergence of opinion. Treatment of inflammatory rectal stricture has been by: 1) drugs and antigens, 2) irradiations, 3) dilatation and 4) surgery. The sulfonamide compounds have been the drugs giving best results. However, drugs and antigens treat the inflammation but not the stricture. Irradiation has been reported to be of little, if any, benefit. Dilatation has had a wide use but is not without danger. Various surgical procedures, aimed at diverting the fecal stream, have been employed but with no great degree of success.

The authors analyze 192 cases treated at the Cincinnati General Hospital during the past 25 years. Eighty six per cent of 105 tested cases gave positive reactions to lymphopathia venereum antigen. In their opinion no single therapeutic measure for the rectal stricture has yet been found. Treatment is governed by the stage of the disease, age of patient, degree of co-operation and response to conservative therapy. In cases of asymptomatic stricture careful hygiene and regular bowel habits have been sufficient to produce successful results in patients for periods as long as twenty years. Radical excision of the rectosigmoid in 35 patients produced satisfactory results without an operative death. This surgical treatment is advocated for use only after conservative methods have failed.—I. M. Theone.

MERKE, F.: *Inborn duodenal stenosis.* (*Helvetica Med. Acta*, v. 11, p. 587, 1944.)

An 8-year-old female with congenital partial duodenal stenosis had normal body proportions and normal ratio of weight to height, but her height was nearly 5 inches under the normal for her age. After duodenenterostomy, the child grew 8 inches during the next 2 years and thus reached her normal height.—Courtesy Biological Abstracts.

GARCIA, J. A.: *Early diagnosis of acute appendicitis in children.* (*Medical Record*, v. 157, p. 485, 1944.)

The author described a sign and symptom which he believes is characteristic of acute appendicitis in children. There is pain and tenderness in the midline and slightly to the left, about halfway between the umbilicus and the symphysis pubis. The pain does not localize or become referred to the lower right quadrant. The pain in this midline region progresses into the pain of a generalized peritonitis. According to the author, this sign of appendicitis is shown in acute cases where the appendix occurs not only in the pelvic region but in other anatomical locations as well.

Acute appendicitis should be suspected and laparotomy performed within 18 hours of the onset of the illness if a child becomes suddenly but not acutely ill, shows no or only little temperature, has no diarrhea and has a negative urine and a normal pulse, complains of pain in the infrumbilical region and shows pressure tenderness either there or all over the abdomen.—H. Stilyung.

PRUITT, M. C.: *Cramp in rectum: Significance, differentiation and treatment with case reports.* (*South. Med. J.*, v. 37, p. 442, Aug., 1944.)

Spasms in the region of the rectum give rise to the painful sensations of rectal cramps. The muscles involved are the levator ani which surround the rectum in the pelvis. The cause for these cramps is unknown. Several associated conditions have been noted and possibly they may constitute exciting factors. Among these are included pregnancy, goiter, gastrointestinal and liver diseases and pathology of the kidney. Diagnosis is fairly simple since the pain is different from that present in such anorectal diseases as hemorrhoids, tabetic anal crisis, anal fissures and diseases of the prostate. While relief usually occurs spontaneously, the patient will be helped by sedatives if necessary, by change in position, hot sitz baths and warm enemas. The important point to be emphasized is that the underlying condition should be sought and treated.—G. Klenner.

PANCREAS

BRUSH, B. E. AND McCCLURE, R. D.: *Hyperinsulinism treated by subtotal pancreatectomy.* (*Ann. Surg.*, v. 120, p. 750, Nov., 1944.)

Two cases showing the syndrome of spontaneous hypoglycemia are presented. In neither could islet cell tumors be found. Subtotal pancreatectomy yielded satisfactory results in both cases, supporting the belief that there was no actual islet tumor. The authors emphasize that large amounts of pancreas must be excised in such cases. In one patient two-thirds of the pancreas was removed, and five-sixths in the other. A high protein low carbohydrate diet for preoperative trial is suggested for diagnostic purposes. Altho a relatively large amount of pancreas was removed in each, the operation was not followed by any obvious digestive or metabolic disturbance.—I. M. Theone.

YOUNG, H. B.: *A case of accessory pancreas in an unusual position complicated by acute necrosis.* (*Glasgow Med. J.*, v. 142, p. 156, Nov., 1944.)

According to Young, an accessory pancreas is found in less than three per cent of the routine necropsies. The case presented is that of a 36 year old male admitted to hospital as a "perforation". The history and clinical picture did not suggest the true condition. Altho the small pancreatic mass had islets of Langerhans, there was no hyperinsulinism. Tenderness was not limited to the epigastrium but passed down the right iliac fossa. The pathology was a simple necrosis without acute edema. No hemorrhage or hyaline necrosis of the vascular walls were noted. The specimen had no duct, therefore the postulation that obstruction was the cause of the pathology is untenable. The author raises interesting speculations relating to the etiology.—F. X. St. George.

EDMONDSON, H. A. AND BERNE, C. J.: *Calcium changes in acute pancreatic necrosis.* (*Surg. Gynecol. Obstet.*, v. 79, p. 240, 1944.)

Determinations were made of the total blood concentration of calcium in patients with pancreatic necrosis, the ratio of diffusible and non-diffusible calcium in patients in whom the serum calcium was found low, and the concentration of calcium in pancreatic tissue of patients dying of acute pancreatic necrosis. In six autopsy cases the concentration of total calcium in and about the necrotic areas was 200 to 1732 milligrams per gram pancreatic tissue. The longer the illness the more extensive was the fat necrosis and the greater the amount of calcium present in the tissue. Blood serum calcium levels below seven milligrams per cent indicated very poor prognosis. Values below nine milligrams per cent were found in 36 out of 50 patients suspected of having pancreatic necrosis. This low level was reached between the second and fifteenth day. Maintenance of a low serum calcium beyond the second week usually was indicative of either some complication or of progression of the disease. As total serum calcium falls the diffusible calcium rises to maintain normal concentrations of physiologically active calcium. Serum calcium determinations should be carried out to differentiate between acute pancreatic edema and acute pancreatic necrosis.—N. M. Small.

METHENY, D., ROBERTS, E. W. AND STRANAHM, A.: *Acute pancreatitis with special reference to x-ray diagnosis.* (*Surg. Gynecol. Obstet.*, v. 79, p. 504, Nov. 1944.)

Acute pancreatitis is suggested by the following roentgenologic signs: tender tumefaction of the pancreas, ileus, and changes in appearance of stomach and duodenum. These changes in appearance are due to the swelling of the pancreas to several times its normal size with subsequent pushing against the greater curvature of the stomach and loss of tonus by the duodenum. The ileus is usually most evident in the upper jejunum and transverse colon. The X-ray signs were present when the patient was first seen and persisted for some

time after blood amylase values returned to normal. The authors had 32 patients at King County Hospital in Seattle for whom the diagnosis of acute pancreatitis was established by various means. In each case the onset of the disease was acute and marked by nausea and vomiting and by epigastric pain with little tenderness. Ruptured peptic ulcer could be ruled out by lack of board-like rigidity while acute coronary thrombosis was ruled out by the normal blood pressure and pulse rate. The patients were too ill to suggest the condition of acute gallbladder disease. An interesting feature was the albuminuria shown by all the patients; absence of albuminuria should therefore make pancreatitis a doubtful diagnosis.—N. M. Small.

LIVER AND GALLBLADDER

ARMSTRONG, C. D., AND CARNES, W. H.: *Obstruction of the hepatic veins (Chiari's disease). Report of five cases.* (*Am. J. Med. Sci.*, v. 208, p. 470, Oct., 1944.)

Obstruction of the hepatic veins has been reported in the literature about sixty times. A variety of etiologic factors has been offered. Alcoholism, syphilis, and mechanical stresses associated with pregnancy or cough were favored by earlier writers but these probably are rare. Neoplasm, polycythemia vera, infections and anomalies are the most frequent causes. Thrombosis occurs most frequently at the site where the hepatic veins empty into the inferior vena cava because the oblique angle of entrance of the vein favors eddy currents. Both sexes are equally affected and range in age from 17 months to 70 years. Most cases occur between ages 20 and 40 years. The acute form appears suddenly and leads to death in one to 4 weeks. The chronic form is gradual in onset and death ensues within periods of six months to several years. Symptoms may not appear until the obstruction has become complete.

The condition is rarely diagnosed during life. The picture is one of portal vein obstruction and hepatic insufficiency. No form of treatment is known or recommended. Surgery has always been fatal. Hepatic vein obstruction should be considered in any patient with progressive tender enlargement of the liver and spleen accompanied by ascites and abdominal pain.—W. D. Beamer.

GILLMAN, J., AND GILLMAN, T.: *Liver in pellagra.* (*Lancet*, v. 247, p. 161, 1944.)

An improved liver biopsy method was used to study the livers of some 100 non-European patients with pellagra and other nutritional diseases. Liver damage in pellagra is reflected by extensive accumulation of fat, which may become absorbed under therapy, and in adults is followed by the deposition of an iron-containing pigment, cytosiderin, in large amounts and which may lead to pigment cirrhosis. This pigment cirrhosis has not been produced yet in animals by dietary methods. In humans suffering from pellagra or other nutritional diseases, despite the low protein content of their

diet, hemorrhage or necrosis of the liver was not observed.—Biological Abstracts.

POPP, L.: *Statistical study of the etiology of hepatic cirrhosis.* (Zeitschr. Klin. Med., v. 142, p. 106, 1943.)

Cirrhotic changes in the liver were found in 450 (3.95 per cent) of 11,337 autopsies performed during 1939-43, at the Pathological Institute of the Allgemeines Krankenhaus St. Georg in Hamburg, on persons over 15 years of age. The pathologic findings are described and tabulated. The male to female ratio was 1.9:1 (319 males, i.e., 5 per cent of total male autopsies; 131 females, i.e., 2.6 per cent of total female autopsies). The incidence is within the range reported by other investigators, whose findings are tabulated, but the ratio is smaller. The highest incidence among males occurred between the ages of 51 and 60; among females, between 61 and 70. Seven of the females and 116 of the males were definitely classified as alcoholics. On the basis of reliable anamneses, 5 to 10 times as many males as females are regarded as given to alcoholic excess; in the present autopsy material, however, only about twice as many males as females had cirrhosis of the liver. This suggests that alcohol is of etiologic importance in only a limited number of cases; on the other hand, alcoholism was the only cause of disease in at least 20 per cent of the alcoholics. Only 40 per cent of the alcoholic patients lived beyond the age of 60, while 60 per cent of all males, and 55 per cent of the males and 71 per cent of the females with cirrhosis of the liver, lived beyond 60. In comparing all males who had cirrhosis with all females who had cirrhosis, great differences were found not only in morbidity but also clinically and pathologically. When the 201 nonalcoholic males with liver cirrhosis were compared with all females who had cirrhosis, great similarities in age and etiologic factors were found between the 2 groups. From this it is concluded that if cirrhosis of the liver is not complicated by alcoholism it seems to be a disease of old age in both males and females. Alcoholic excess is of fairly high secondary significance for the patient with cirrhosis of the liver. The clinical manifestations are more distinctive in the inebriate; ascites and icterus are more frequent, and the diagnosis is more easily made. "Alcoholic excess due to its influence on the clinical picture, is overestimated as an etiologic factor; cirrhosis of the liver in the alcoholic is due, in general, to the same causes as in the nonalcoholic. Only fatty cirrhosis is a definitely alcoholic cirrhosis." Other etiologic factors, including infectious diseases, jaundice, diabetes, chronic biliary disease, hematologic diseases, and endocrine changes, are discussed.—Courtesy Biological Abstracts.

GOODELL, J. P. B., HANSON, P. C., AND HAWKINS, W. B.: *Protection against liver damage from arsenicals by protein feeding.* (J. Exper. Med., v. 79, p. 625, June 1944.)

Following arsenical therapy there is often a resulting complication of liver damage. Liver damage has also been observed and produced experimentally, following

the use of other drugs. High carbohydrate diet has been used to both arrest liver damage and restore a liver already damaged. The authors conclude that the beneficial effects of the high carbohydrate diet are due to the protein-sparing action of the carbohydrate. They believe that adequate protein intake is of the utmost importance. Dogs were given an arsenical preparation in large doses. Animals which had their protein stores depleted by restricted protein intake showed evidence of liver damage, such as a high icterus index. On the other hand animals with adequate protein stores showed no evidence of liver injury even when larger doses of the arsenicals were given. The authors recommend high protein levels to protect the liver against toxins and particularly in patients who must receive arsenical therapy. —D. A. Wacker.

ULCER

COPELLO, O.: *Gastro-duodenal ulcer in the newborn.* (Anales Dispers. Publico Nacional. Enferm. Aparat. Digest., p. 811, v. 6, 1943.)

A full discussion is presented on gastro-duodenal ulcers in children; symptomatology, pathology, treatment and incidence of occurrence are given. The author stresses the point that acute ulcer of the stomach or duodenum in the newborn is frequently overlooked. For this he offers two explanations: first, the ulcer occurs usually as secondary to an acute infection and second, clinicians on the whole seem unaware of the possibility of its occurrence. Melena neonatorum and anemia in the newborn are often due to these ulcers. A variety of treatments are outlined and evaluated by Copello.—D. I. Abolafia.

NONNENMACHER, M.: *Reliability of roentgenologic diagnosis of gastric, duodenal and jejunal ulcer.* (Radiol. Clin., v. 11, p. 277, 1942.)

One hundred and fifty four cases of ulcer trouble were controlled as to the reliability of the X-ray diagnosis before the operation and the result of the control compared with results in literature. In the author's material, the diagnosis for gastric ulcer was correct in 92 per cent of the cases, for ulcus duodeni in 96 per cent and for ulcus pepticum jejunii in 33 per cent only. —Courtesy Biological Abstracts.

FERRER ZANCII, A. G., AND BONDUEL, A. A.: *Transective duodenal ulcer.* (Rev. Asoc. Med. Argentina, v. 58, p. 337, 1944.)

Epigastric injury was held to be the cause of duodenal ulcers in a 45-year-old carpenter, compensable as a 40 per cent disability.—Biological Abstracts.

SCHIFF, L.: *The treatment of bleeding peptic ulcer.* (Cincinnati J. Med., v. 25, p. 187, 1944.)

The literature reports the incidence of bleeding in peptic ulcer to be between ten and sixty per cent. Possibly due to the stress of war the incidence of hemorrhage is increasing. Situated on the posterior wall of the superior portion of duodenum, the bleeding ulcer is generally due to erosion of an artery at its base.

Relaxation and allay of fear and emotion are essential for good response to treatment. Restlessness may be controlled by sedation; phenobarbital is preferred to morphine because of the nausea and vomiting which morphine may produce. Free use of fluids is permitted to help maintain blood volume; if oral fluid intake is impossible then hypodermoclysis or intravenous drip may be employed. Blood transfusion, contrary to earlier opinions, does not elevate blood pressure to produce increased hemorrhage. Blood transfusion is very definitely indicated when the blood loss has been extreme. Iron is prescribed, preferably only after cessation of tarry stools. The patient should be fed well and promptly. The diet is selected with several items in mind, including adequate caloric value as well as vitamin C, mineral and salt content. The patient, both subjectively and objectively, does better on a prompt feeding regimen than he would if the older starvation routine were employed. In 160 patients studied by Schiff, the gross mortality was 6.8 per cent when measures advocated by him were used. This is in contrast with a mortality rate of about 25 per cent obtained by the older starvation regimen. Hospital stay was likewise reduced from 32.4 days to 25.6 days. Schiff mentions that in spite of the excellent results obtained from the prompt feeding program, a few individuals remain whose bleeding can be controlled only by surgery. Surgical intervention must be done early in the emergency since the mortality rate increases with delay in surgical treatment.—N. M. Small.

THERAPEUTICS

EMERSON, K. JR., AND BECKMAN, W. W.: *Some effects of the administration of amino acids in a patient with idiopathic steatorrhea.* (*J. Clin. Invest.*, v. 23, p. 937, Nov., 1944.)

A patient with idiopathic steatorrhea, hypoproteinemia, and hypocalcemia, was given amino acids in the form of an enzymatic hydrolysate of casein. The hydrolysate replaced an equal amount of the daily dietary protein and was administered intravenously as a 10 per cent solution. After two days of this treatment the diarrhea ceased and during the following week the patient showed a marked retention of nitrogen and a decreased output of fecal and urinary nitrogen. Phosphorus and calcium excretion remained unchanged.

Four days after cessation of this treatment diarrhea reoccurred and the patient was given 45 gram of amino acid mixture orally. This was administered daily for one week and again the stools returned to normal and nitrogen retention occurred. Also there was an increase in retention of calcium and phosphorus which did not occur during the course of intravenous treatment.—G. N. W. Smith.

CONSALES, P. A., AND O'CONNELL, W. T.: *The use of blood in the treatment of duodenal fistula.* (*New England J. Med.*, v. 231, p. 582, 1944.)

As operations in the right upper quadrant become more frequent, development of external duodenal fistula as a complication becomes more frequent. The mortal-

ity rate has been reported to be as low as 23 per cent but 50 per cent is a more common figure. Attempts at neutralizing the intestinal contents in the region of the fistula have proved rather unsuccessful. In the case reported all the usual methods of treatment were tried but without benefit. However, rapid healing occurred when cotton packs soaked in freshly drawn autogenous blood were applied repeatedly to the fistula opening. This procedure is advocated for more extensive trial.—G. N. W. Smith.

HART, B. F., McCONNELL, W. T., AND PICKETT, A. N.: *Vitamin and endocrine therapy in nausea and vomiting of pregnancy.* (*Am. J. Obstet. Gynecol.*, v. 48, Aug., 1944.)

Pyridoxine hydrochloride given intravenously brought complete relief to 23 patients and partial relief to 13 patients with nausea in early pregnancy while 7 patients were not benefitted. When thiamin was added to the pyridoxine that was being administered, complete relief was obtained in 46 cases, partial relief in 11 cases, and 9 were not benefitted. Adrenal cortical extract was given to five of these nine failures with decided improvement in three. If the first injection did not prove effective, continuation of the therapy proved without avail. It was observed that vitamin therapy was of greater benefit in primigravidas than in multigravidas. The reason for the greater percentage of successes among primigravidas is unknown but it is conjectured that it may be linked to fat metabolism. The effect of the adrenal cortical extract is believed to be due to its effect in increasing the activity of thiamin.—N. M. Small.

SURGERY

BISGARD, J. D., AND OVERMILLER, W.: *Emergency gastrectomy for acute perforation of carcinoma of the stomach; with diffuse soiling of the free peritoneal cavity.* (*Ann. Surg.*, v. 120, p. 526, Oct., 1944.)

Although occurring infrequently, acute perforation of carcinoma of the stomach into the free peritoneal cavity has been a complication of gastric carcinoma. Upon the basis of generally accepted standards about half of the cases of perforating gastric carcinomas are such which would be considered resectable. In many perforated carcinomas the presence of a neoplasm has been missed at operation. Routine examination of biopsy specimens from the edge of all gastric perforations should be done to reveal possible neoplasms. When possible, emergency primary gastrectomy is the operation of choice. The authors were able to find 217 cases of perforated gastric cancer described in the literature and add a case of their own.—F. X. Chockley.

EXPERIMENTAL MEDICINE

MOTILITY

DE GENNARO, A., AND BERTOZZI, C.: *The effect of Priscol on the motility of the stomach and intestines.* (*Bull. Soc. ital. biol. sper.*, v. 17, p. 469, 1942.)

Priscol (2-benzyl-4, 5-imidazoline hydrochloride) was found to increase both tonus and motor activity of

the stomach in man. Similar results were found for the rabbit but the colon was much less affected. The increased motor activity in the rabbit's stomach lasts little more than half an hour. Atropine antagonized the effects. Similar effects were obtained with nicotinic acid and with histamine, the former being somewhat less pronounced than Priscol.—C. Foderaro.

ABSORPTION

LASZY, L.: *Influence of vitamin D on the blood sugar in man.* (*Helvetica Physiol. Pharmacol. Acta.*, v. 1, p. 44, 1943.)

Five individuals were given 50 grams of glucose and their carbohydrate tolerance curve determined for one hour. Individual differences were observed in each case. However these differences were wiped out when the glucose tolerance tests were preceded by taking very large doses of vitamin D concentrates. The vitamin D apparently increased glucose absorption but apparently not by merely increasing intestinal permeability in general.—D. A. Wocker.

LOUGHLIN, E. H., BENNETT, R. H., FLANAGAN, M. E., AND SPITZ, S. H.: *Studies on the absorption of sulfonamides from the gastrointestinal tract.* (*J. Lab. Clin. Med.*, v. 29, p. 921, Sept., 1944.)

The experiment was carried out on two groups of albino rats, the first group having just had the pylorus occluded, the second group being normal. In both groups the sulfonamides were administered by gavage and blood samples, obtained by cardiac puncture, were taken on the normal rats 5 minutes after administration of the drug and every 5 or 10 minutes for the next hour. From the rats with pyloric occlusion blood specimens were taken every minute during the first 5 minutes after administration.

Results showed that in both groups, conjugated sulfonamides were found in the blood 5 minutes after administration, although conjugation occurred in some rats as early as 1 minute after administration. The degree of conjugation was found to be greater when the sodium salts of the sulfonamides were administered. In those rats of both groups that received sulfapyridine and sulfadiazine, the free and total blood levels ran closely parallel. However, the free and total levels of the normal group of rats which received sulfathiazole showed moderately wide divergences. It was found that sulfapyridine, sulfathiazole, sulfadiazine and their sodium salts are absorbed in significant amounts from the stomachs of albino rats, though much greater quantities of sulfonamides (sulfadiazine excepted) are absorbed from the gastrointestinal tracts of the rats without pyloric occlusion.—R. L. Burdick.

PATHOLOGY

TEDESCHI, C. G.: *Gastric mucosal lesions in rats submitted to head trauma.* (*Proceed. Soc. Exper. Biol. Med.*, v. 57, p. 268, Nov., 1944.)

Rats were submitted to routine procedures which resulted in traumatization of their heads. The blows, both as to number and intensity, were standardized.

Damage of the gastric mucosa was found. This consisted of dissemination of tiny hemorrhages which aligned themselves along crests of gastric plicae. In general these hemorrhages were superficial and assumed a simple pattern. Definite erosions were seen infrequently and these did not penetrate deeper than the layer of mucosa. The hemorrhages were confined to the stomach proper and affected all portions of the stomach with equal frequency or intensity. Some correlation was noted between the severity of the trauma to the head (and of the cerebral damage incident to trauma) and the occurrence of gastric changes. When the acute effects of the trauma did not kill the animal, it was found that the gastric mucosal damage showed a tendency to prompt and complete healing.—M. H. F. Friedman.

HIMMSWORTH, H. P., AND GLYNN, L. E.: *The prevention of experimental massive hepatic necrosis by methionine.* (*Clinical Science*, v. 5, p. 133, 1944.)

Massive hepatic necrosis may be produced by dietary means as a deficiency disease due to lack of a protein component. This type of hepatic necrosis may be prevented in rats by feeding the diet plus methionine. In place of methionine 8 per cent casein may be included in the diet; the efficacy of the casein has been shown to be due to its methionine component and probably no other.—B. Adolph, Jr.

HIMMSWORTH, H. P., AND GLYNN, L. E.: *Massive hepatic necrosis and diffuse hepatic fibrosis (acute yellow atrophy and portal cirrhosis).* (*Clinical Science*, v. 5, p. 93, 1944.)

In the rat liver there can be produced two distinct pathological lesions by means of appropriate diets. One lesion is massive hepatic necrosis which resembles the condition of "acute yellow atrophy" in man. The other lesion is diffuse hepatic fibrosis closely resembling human portal cirrhosis. Diets rich in fat, and also diets devoid of fat but poor in lipotropic factors, both lead to diffuse hepatic fibrosis with fatty infiltration. Probably the fatty infiltration of the liver precedes and eventually leads to diffuse hepatic fibrosis. The massive hepatic necrosis is produced by low-protein diets and is due to the lack of some essential component of protein, possibly an amino acid.—B. Adolph, Jr.

HANDLER, P.: *Alleviation by raw liver of anorexia produced by sulfapyridine.* (*Proceed. Soc. Exper. Biol. Med.*, v. 57, p. 99, Oct., 1944.)

Sulfapyridine fed to rats produced a reduction in the appetite and the growth rate. The growth failure was due largely to the relative anorexia. Whole liver powder and concentrated liver extract were without effect in this connection but raw liver increased both appetite and growth rate. Sulfapyridine was also fed four dogs on a standard diet. Food consumption was found to be cut down by 58 per cent. Raw liver was found to alleviate the anorexia. The explanation for the beneficial effects of raw liver is still to be found but possibly the sulfapyridine produces anorexia by interfering with nicotinic acid metabolism.—M. H. F. Friedman.

ZUCKER, T. F., AND BERG, B. N.: *The time factor in the production of gastric lesions on low calcium diets.* (*Proc. Soc. Exper. Biol. Med.*, v. 57, p. 1, Oct., 1944.)

Gastric lesions, confined exclusively to the mucus-secreting non-acid portion of the stomach, develop in four weeks on rats kept on a low calcium diet. Development of the lesions may be prevented by returning the rat to normal dietary calcium.

In rats kept for periods longer than four weeks on low calcium diets the ulcerative lesions were found to be accentuated as were too the hemorrhagic and hyperplastic character of the lesions. There also developed a generalized tendency to bleeding. However, although the ulcerations became more extensive they did not become deeper so that they did not penetrate but remained superficial. In addition to ulcerations and generalized bleeding, loss of hind leg function developed towards the eighth week of the low calcium diet and about half of the animals were either moribund or dead.
—M. H. F. Friedman,

MISCELLANEOUS

SHEPLER, J. R., AND YOUNG, C. L.: *Parietal pain.* (*Military Surg.*, v. 95, p. 179, Sept., 1944.)

Pain or tenderness in the lower right abdominal wall due to hypersensitivity of the skin, fascia, muscle or peritoneum constitutes parietal pain. Basically this,

is a neuralgia similar to that of neuralgia of other organs. The true etiology is still unknown: several possible factors have been suggested as being partly or wholly responsible. Inflammation or pressure of a spinal nerve, lordosis, diseases, toxemias, tumors and scoliosis have been considered as possible causes. Many of the patients show scoliosis. Acute attacks of parietal neuralgia occur usually in association with some infection, particularly of the upper respiratory tract. Parietal neuralgia should be kept in mind when signs and symptoms are being considered for a diagnosis of appendicitis.—G. Kleiner.

VUGCORF, I. J.: *Spontaneous rupture of rectus abdominis muscles; result of indirect muscular effort.* (*Am. J. Surg.*, v. 66, p. 132, Oct., 1944.)

Sudden muscular contraction, such as in scaling a wall in the obstacle course of military training programs, may constitute a sufficient degree of indirect violence to rupture the rectus abdominis muscle in susceptible individuals. Three cases of spontaneous rupture of the right muscle are recorded as having occurred in young men who were in military service only one month. Conservative treatment yielded good results. Cases of injury of deep epigastric vessels with resulting hemorrhage should be considered for surgery.
—F. X. Chockley.

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The Pathology of Regional Ileitis

By

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REGIONAL ILEITIS AS A CLINICAL AND PATHOLOGICAL ENTITY

UNTIL recently the disease known as *regional ileitis* has been an almost unrecognized condition; but it has latterly been popularized as an entity for diagnosis, through the considerable attention which it has received in medical literature. This is fortunate, because a sufficiently early recognition of the condition may save the patient from prolonged unnecessary illness and from the ultimately fatal outcome of the disease process.

This communication aims at filling in some of the many hiatuses that are still present in our knowledge of the pathology of the disease. Perusal of the literature on this subject provides a patchy, though otherwise fairly complete, picture of the clinical features of regional ileitis; but the microscopic pathology of the lesion still presents a confused variety of isolated pictures, instead of a comprehensive whole, leaving us completely in the dark as to the aetiology, biology or pathogenesis of the condition. Some new theories relating to this aspect of the matter will therefore also be presented along with a detailed consideration of particularly the micropathology of the condition.

CURRENT LITERATURE ON THE SUBJECT

This disease has been described under a variety of names, but is best known today as *regional ileitis* or *Crohn's disease*. Crohn's original paper was a joint effort by himself and his colleagues Ginzburg and Oppenheimer. Thereupon Moschcowitz emphasized (1940) that the chief contribution of Crohn and his collaborators was to identify and describe a very specific entity from a group of related non-specific granulomata of the intestine. Several hundred cases have since been placed on record in many different papers chiefly contributed from America; but it is noteworthy that such reports have come from all parts of the world. Many cases are undoubtedly met with in practice without being reported, for the condition appears to be at least half as common as *ulcerative colitis* (Crohn, 1939).

A search through neglected archives has enabled Sherrill and Hall (1940) to trace the origin of our knowledge regarding intestinal granulomata to a paper by Combe and Saunders in 1806, followed by a contribution from Abercrombie in 1828. The earliest writers of the present century are Moynihan (1907), Braun (1909), Tietze (1910) and Dalziel (1913).

The paper by Crohn, Ginzburg and Oppenheimer (1932) crystallised *regional ileitis* as a clinico-pathological entity distinguishable from, though possibly still related to, the remaining confused moiety of intestinal granulomata. It further served an excellent purpose in

stimulating an interest in the disease state, so that numerous contributions immediately followed. It is often remarkable how several scientists find themselves unwittingly interested in the same subject at the same time. The problems presented by *regional ileitis* were no exception to the rule and several of these early contributions immediately preceding or following Crohn's classical paper, made no reference to his leadership in the matter, which probably means that the pathological state was suddenly and simultaneously manifesting itself in a sub-epidemic manner in different quarters. In fact, a recent analysis by Brown & Donald (1942) shows that the disease is appearing more frequently.

Spruill (1936) and Jellen (1937) each reviewed these early publications, the former summarising the known facts about altogether 123 cases. His contribution was the more valuable in that it correlated the variety of findings characterising this disease, as well as sifting the different emphases of individual workers.

By now knowledge about the pathological anatomy had outstripped the clinical studies. Confusion was beginning to arise in regard to various clinical phases of the disease. The position was much clarified by Mixter's review in 1939, which clearly delineated the different stages of the disease. Since then interest has shifted to the elaboration of problems of Roentgen diagnosis, originally tackled in a convincing manner by Kantor (1934), and to the question of the correct treatment during various phases. While reading the newest literature on the subject one inevitably comes to the conclusion that a great many facts about the pathology of this disease are being taken for granted, even when it is self-evident that more detailed studies of the clinical and micropathology are most likely to provide a clue to the solution of the baffling problem of the aetiology of the disease.

NOMENCLATURE

The name *regional ileitis* seems to have become stabilized for this disease, but different terms are still being used. It is certain that the lesion may affect virtually any part of the intestinal tract and may ultimately involve all parts of the abdominal cavity, as Crohn himself reported (1939), but in the large majority of cases so far the disturbance seems to have originated in the terminal ileum. To add *terminal* to the name (Bockus and Lee, 1935) would appear however to define too meticulously. To substitute *enteritis* for *ileitis* (Mixter, 1939, Meyer and Rosi, 1936, Lewisohn, 1938) puts the wrong emphasis. The term *segmental enteritis* (Lewisohn, 1938) appears to have no advantage over *regional ileitis*.

The same criticism applies to the use of the appellation *localised hypertrophic enteritis* (Jackman, 1934),

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or *hypertrophic jejuno-ileitis* (Schapiro, 1934), or *ileocolitis* (Erb and Fermer, 1935). An elaboration of the early term *chronic interstitial enteritis*, introduced by Dalziel (1913) would have had useful application. The use of *ileitis terminalis stenosans* (Slany, 1940) omits reference to the most characteristic feature, namely the regional or segmental distribution. Many of the earlier papers referred to the condition as being a type of *granuloma of the intestine* (Oldsworth, 1933), its non-specific character having been stressed at this stage. (cf. Binney, 1933, Moschcowitz and Wilensky, 1927, Colp, 1934, Erdman and Burt, 1933). Mock (1931) was more certain of the "infective" nature of the granuloma, while Jefferies (1928) prudently referred to the condition as inflammatory. The term *chronic cicatrising enteritis* (coined by Harris, Bell and Brunn, 1933) has been favoured until quite recently, (cf. Mixter, 1939, Barbour & Stokes, 1936, Douchess and Warren, 1934). But the condition is not initially cicatrising in effect and almost always passes through acute and subacute phases. Finally, laudable as the suggestion in Hurst and Lintott's use (1939) of Crohn's disease as a descriptive term may be, experience has shown that such a practice usually leads to the terminology being disputed at a later stage, with resulting confusion when the new name is introduced. It seems wiser, therefore, to retain the already more popular name *regional ileitis*.

EPIDEMIOLOGY

Although about half as frequent in its incidence as ulcerative colitis, still not sufficient facts are known about the epidemiology of the disease, because this aspect of the matter is often slurred over in clinical reports. In his recent review Crohn (1939) states that males of the third to fourth decades are more frequently attacked than females. Clark (1938) and others claim, however, that it is a disease of young males and an analysis of 71 proved cases carried out by Wirts & Lyon (1941) gives the average age for acute cases as 23 years and for advanced cases 29 years. Actually all age groups may be affected, and occasionally more than one in the same family. One patient, described by Moschcowitz (1940), was of the Loraine-Levy endocrinopathic type. This disease shows no racial preference, as it occurs in all parts of the world. Spontaneous cure may happen in the acute phase so that the disease does not necessarily advance to the chronic stage (Wirts & Lyon, 1941). But once the condition has become chronic, recovery can only be effected by means of surgical resection, recurrence taking place in from 7.7% (Crohn, 1939) to 20% (Mixter, 1939) of cases, "owing to the failure on the part of the surgeon to eradicate the whole intestinal lesion". This fact alone suggests a specific and in chronic cases persistent pathogenic agent in the bowel. The higher the lesions are localized in the intestinal tract, the more virulent does the condition appear to be (Mixter, 1939). In these acute cases fatal perforation may occur, although the intramural abscesses, typical of the condition, more frequently lead to fistulae, whose immediate effects are less dangerous and may even afford temporary relief from other symptoms. Intestinal obstruction may oc-

casionally also be found in acute cases (Jackman, 1934). Stenotic signs are more typical, however, of later stages. Before death supervenes in these chronic cases, sometimes only after 15 years, the continuously ill patient may develop all manner of fistulous tracts (internal, external, rectal, recto-vaginal, recto-vesical and ischiorectal), may suffer from pelvic peritonitis, abscesses and finally general peritonitis. Or he may waste away from marasmus, nutritional disturbance and anaemia (Crohn, 1939) assisted by chronic diarrhea and occult and even massive haemorrhage. Not infrequently surgical treatment anticipates the termination of the sufferer's miserable existence.

AETIOLOGY

Much less positive information is at hand regarding the aetiology of this disorder. Confusion arises when pathological and reactive mechanisms are not clearly defined from purely pathogenic factors. Owing to the manifest inflammatory nature of the lesion, diligent search has been made in the past decade for an *infective* aetiological factor. Crohn, Ginzburg and Oppenheimer (1932) could find no causative organism at all. Mock's (1931) cases were similarly sterile. A search for acid-fast bacilli was equally fruitless in the hands of Hadfield (1939), Sproull (1936), Jellen (1937) and Schapiro (1934). Some cases are so similar to intestinal tuberculosis, that the latter author still favoured diagnosing primary tuberculosis of the intestine at that time. Non-motile *B. coli* were isolated by Erb and Farmer (1935) and streptococci of the alimentary type by Jackman (1934) in the surface exudate of acute cases; and anaerobic avirulent streptococci were cultivated from ulcers by Mixter (1935), but did not fulfill Koch's postulates for causative organisms in being able to cause similar lesions in experimental subjects. Late-ly Chapin and Crohn (1939) have postulated a relationship to bacillary dysentery on circumstantial evidence only. A *streptococcus viridans* theory arose recently. Mailer (1938) investigated for this organism, finding it in the throat only. Most convincing of these investigations into positive infective organisms is that by Pumphrey (1938), who found no pathogenic, fungal or parasitic organisms after careful and exhaustive search. Despite this all round failure to discover a responsible organism Hadfield (1939) inclines to share the view with Crohn (1939) that the lesion resembles that caused by *Boeck's sarcoidosis*, and the former suggests that the two may still be shown to have a single pathology and aetiology. This would be true in a degree if Crohn's conclusion that the lesion may represent a non-specific reaction to a multiplicity of possible agents, were correct. Crohn does suggest that an infective agent may have been overlooked owing to its restriction to a regional zone of lymphadenitis.

Clinical pathological studies bearing on the aetiology have added hardly anything to our knowledge of a possible biological origin of the disorder. Inconstant anaemia and inconstant leucocytosis have been observed from time to time by Mixter (1939). Where anaemia occurs it is of the low colour index type and leucocytosis is due to excess of neutrophil polymorphonuclear

leucocytes, lymphocytes actually being reduced in number. Negative Wasserman, Rosenthal, Widal, Pirquet and Mantoux reactions and negative stool and blood cultures have been recorded by various observers. In one case Moschcowitz (1940) also records the presence of a slight bacteriophage for the Mt. Desert strain of dysentery bacillus, a flat curve for the Jenny test, and a normal curve for the Rehfuss test meal. Baird (1940) also found the *gastric analysis* normal, but Siris (1941) records achlorhydria in his cases. *Bloodchemistry* examinations by Siris and by Moschcowitz revealed blood sugar of 75 to 90 mgm %, blood urea nitrogen of 11 to 17 mgm %; blood calcium 10 mgm % and cholesterol values of 140 to 155 mgm %. Little as these studies reveal, their pursuance seems to indicate a welcome departure, as biochemical and biophysical aetiological factors have as yet received too little attention.

Trauma as a factor has been observed in some of his cases by Mock (1931) and he suggested that the sequence of reactive changes is such as may follow on a vascular disturbance with slow necrosis, inflammation and repair.

Trauma may take the form of injury by means of a fishbone or an ingested pin, according to Ralphs (1938), though he has not actually seen such foreign bodies, nor has anyone else reported them. Irritation from *reflux through the ileocaecal valve*, owing to mechanical defect or reversed peristalsis, has not yet been postulated, but may be implied in the suggestion by Baird (1940) that chronic ulcerative colitis may involve the terminal ileum by retrograde extension. Another possible source of injury or irritation may result from *repeated self reducing volvulus or intussusception*, as suggested by Coffey (1938) and others. But if this were actually to occur, the vascular supply would suffer early, so that partial or temporary ischaemia would be the main factor to be considered, as suggested by Mock. *Stagnation at the ileocaecal valve* might lead to absorption of a noxious agent, according to Mixter (1939), who clings to the belief that a relationship exists between regional ileitis and appendiceal pathology, dysentery, lymphogranuloma and mesenteric lymphadenitis. This list has been extended recently by Sherrill and Hall (1940) who postulate that regional ileitis may even be a predecessor for intestinal sarcoma. The presence of *ingested inert foreign bodies* as a causative agent has been postulated by Meyer and Rosi (1935); *lipoids* have been recognised in giant-cells by Homans and Hass (1933) while Sailer and McGann (1942) have investigated the lipophagic characters of certain types of intestinal granulomata suggesting that the presence of the lipoid is secondary and not etiological in significance. The only remaining theory, namely that of *lymphatic block*, of which the chief exponent was Jackson (1937), is discredited by Crohn (1939), despite the experimental evidence in its favour, introduced by Reichert and Mathes (1936), who showed that lesions similar to those of regional ileitis may be produced in the bowel of experimental animals by the injection of irritating solutions into the mesenteric lymphatics.

CLINICAL FEATURES

Three or four clinical stages or phases have been recognised by different authors (Harris, Bell and Brunn, 1933; Meyer and Rosi, 1936; and Mixter, 1939). The acute phase, first clearly defined by Jackman (1934) stands apart as a separate clinical entity distinct from the other phases, in so far as it is almost impossible to isolate it from other causes of acute abdomen and as it is the only time when spontaneous cure may take place, the lesion actually healing more often than it progresses to chronicity, (Smithy and Charlston, 1943). Such an acute case has been described in a child of two and a half years, by Erb and Farmer (1935), and has more recently been seen in even younger infants. Judging by the complete degree to which healing may take place in cases not complicated by extensive ulceration, and taking cognisance of the fact recorded by Jackman that even acute cases may be superimposed on cicatricial tissue suggestive of healed lesions, the possibility emerges that mild acute cases are amongst some of the causes of undiagnosed abdominal pain and pyrexia in young children, or that the scars of self-resolving volvulus or intussusception may facilitate the appearance of regional ileitis in later life.

Having survived this first phase of acute abdomen or stage of peritoneal irritation characterised by pain in the iliac fossa, fever and spasm, the disease may progress through a sub-acute to a chronic stage with three major phases.

The first phase, as Mixter (1939) has shown, may easily be confused with ulcerative colitis, being characterised by diarrhoea and the passage of mucus and sometimes blood; cramps, without tenesmus, occur; perianal lesions appear; bouts of fever, weakness, and loss of weight are almost always associated with this phase, when intramural ulceration dominates the pathological picture. This phase, according to Crohn (1939) may last from one to fifteen years, the patient rapidly or gradually going downhill.

The next phase begins when stenosis supervenes. The clinical features are therefore those of chronic partial intestinal obstruction, namely, colicky abdominal pains, distension, nausea, vomiting and constipation alternating with diarrhoea (Mixter, 1939).

The last phase, on the other hand, namely that of fistula formation, may commence early, and the presence of these various types of fistula may so dominate the clinical picture that the main disorder may go unrecognised.

The physical findings are not distinctive enough to merit description. The presence of a palpable mass in the right iliac fossa, when associated with the above symptom complex, usually necessitates laparotomy and surgical resection. The only certain guide pre-operatively is X-ray examination, when the "string sign" of Kantor and other well-known features may be displayed.

These are some of the main clinical features of the classical cases. The disease knows many, though rather unexpected, variations, so that diagnosis may be rendered impossible.

II. CASE REPORT AND GROSS PATHOLOGICAL ANATOMY

History

The patient, a middle-aged male subject, who had no previous history of relevant abdominal symptoms and, as far as is known, was subject to no immediately pre-existent or predisposing condition, suddenly became ill with moderate abdominal colic and developed pain in the right iliac fossa, which persisted and was accompanied later by fever, and complicated by diarrhoea and the passage of mucus. After several weeks, a palpable mass in the right iliac fossa, and this history, induced Dr. J. du Toit le Roux, of Adelaide, South Africa, to perform laparotomy. He excised the diseased region widely and effected an end to end anastomosis. Uneventful recovery occurred, but was succeeded after some months by recurrence of the symptoms, the advent of cachexia and ultimate death.

GROSS PATHOLOGY

The portion of the intestine which was affected (Fig. 1) measured about ten inches in length and consisted of the terminal ileum, a few inches from the ileo-



Figure 1. Photograph of the affected segment immediately after its resection. (Taken by Dr. du Poit-le Roux.)

- (a) Distal limit of the lesion.
- (b) Contraction of the mesentery and kinking of the ileum.
- (c) Proximal limit of the lesion delimited by means of a ligature.

caecal valve. The part was kinked on itself at the middle, as in the case described by Siris (1941) where the cause was likewise constriction of the mesentery (Fig. 1 c). A diverticulum projected from it towards the ileum about two inches above the proximal limit of the lesion. It was found to be about an inch deep. The lesion was seen to be sharply delimited in its proximal and distal extensions (Fig. 1, a & c), corresponding to the condition found by Jackman (1934) and unlike the condition described by Mixter (1939) which gradually shaded off into normal bowel. The appendix was normal and no other areas were seen to be involved. In its position and size the lesion was therefore more or less typical. (cf. Crohn, 1939). The proximal portion of the lesion was thinner than the distal part. The former represents the youngest lesion according to the views of Crohn, Ginzburg and Oppenheimer (1932) and Bockus and Lee (1935) who found that the lesion develops disto-proximally as it expands. No ballooning of the gut, proximal to the lesion, such as observed by Barbour and Stokes (1936), Erdmann and Burt (1933), Harris, Bell and Brunn (1933) and Jackman (1934), was observed at the time of operation, though the presence of the proximal diverticulum may sug-

gest some such effect appearing from time to time. The whole affected area appeared typically swollen, oedematous, patchily reddened, (cf. Sproull 1936), stiff, with a granular rough serosa, whose gloss was typically absent, as described by Crohn, Ginzburg and Oppenheimer (1932), and mesenteric fat appeared to be growing round the bowel in most situations. No adhesions, as described by Colp (1934), were seen and congestion was in evidence proximally, i.e. at the acute region as suggested from the descriptions of Jackman (1934) and Mailer (1938). The rest of the peritoneum presented a mottled white appearance, mottling representing sites of subperitoneal and petechial haemorrhage. No fibrosis or nodularity of the lesion, typical of the late chronic stage (Meyer and Rosi, 1936) could be seen from outside. There were no signs of surface exudate.

The mesentery was typically greatly thickened (Jellen, 1937) and fibrotic (Crohn, Ginzburg and Oppenheimer, 1932). The mesenteric lymph glands observed by Harris, Bell and Brunn (1933) were not in evidence. Nor were the regional lymph glands found enlarged, hardened or fixed, and no biopsy specimen was therefore taken. This corresponds to the cases cited by Barbour and Stokes (1936) and Colp (1934). Regional lymph glands are more commonly found to be enlarged, succulent and oedematous in acute (cf. Erb and Farmer, 1935) and sub-acute cases (cf. Sproull, 1936; Crohn, 1939). Studies by Hadfield (1939) have, however, shown that they indicate histological changes without being necessarily macroscopically affected. Mesenteric blood vessels were conspicuous, but not varicose, as described by Sproull (1936). Incision of the mass revealed that the wall was greatly thickened throughout, due to oedematous tissue proximally, as described by Erb and Farmer (1935) for acute lesions, and owing to infiltration distally. Fibrosis was present, especially in the serosa and submucosa more distally, suggesting that this region represented the chronic lesion, as described by Sproull (1936). Similar to the condition described by Bockus and Lee (1935) the thickness increases proximo-distally, measuring more than an inch in the distal portion, though half of this was admittedly due to fatty tissue in the adventitia. The submucosa alone measured half an inch here. The individual layers could still be fairly well defined in most parts. Mixter (1939) described this condition in the second stage of the disease. No necrotic centres, such as recorded by Erb and Farmer (1935) in their acute case, were seen, nor had the lesions any consistently focal character, as described by Crohn, Ginzburg and Oppenheimer (1932) for late phases of the disorder.

The lumen was narrowed throughout the affected part, as described by Sproull (1936), being most stenosed distally. Hadfield (1939) attributes this stenosis to submucous oedema. Lewisohn (1938), however, has shown that it persists after healing has taken place.

Inspection of the mucosal surface (Fig. 2) shows several typical features. Most obvious is the complete obliteration of transverse folds and villi, and their substitution by broad, solid, longitudinal ridges studded

with various nodules and small papillomata (Fig. 2a). The broadest and most continuous of these ridges occurs opposite the mesenteric border (Fig. 2b). It is interrupted here and there by deeply penetrating sinuses (Fig. 2c), and flanked by serpiginous ulcers. The

along the line of mesenteric attachment. (cf. Crohn, Ginzburg and Oppenheimer, 1932; Binney, 1935; Sproull, 1936; and Mixter, 1939).

The mucosal appearances of regional ileitis are therefore unique.

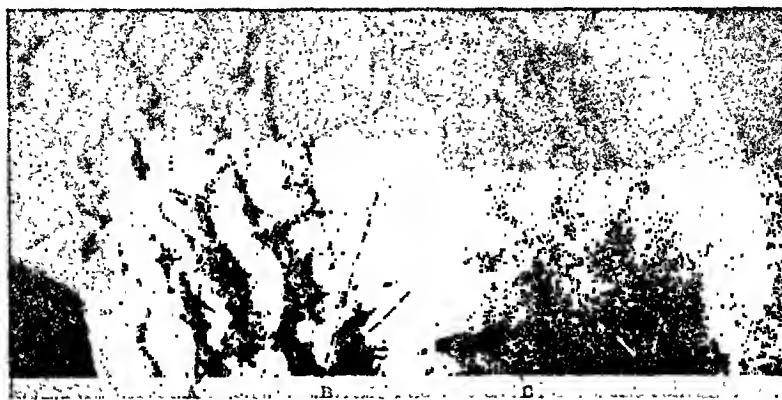


Figure 2. Photograph of the mucosal aspect of the affected segment.

- (a) The longitudinally arranged rugae.
- (b) The longitudinal elevation along the line of mesenteric attachment with cobblestone effect over its surface.
- (c) Opening of sinus penetrating into the bowel wall.

surfaces of the papillomata and ridges show extensive loss of epithelium.

Similar obliteration of transverse folds and villi and the presence of longitudinal ridges has not been described before, though it no doubt occurs in other cases where submucosal swelling appears. The transverse ridges are still present, however, in the case figured by Baird (1940) which may represent a healing primary lesion, thus accounting for their re-appearance. It is not clear from the literature whether the cobblestone appearance originally recorded by Crohn, Ginzburg and Oppenheimer (1932) and subsequently referred to by Jellen (1937) and Mixter (1939) in chronic cases, corresponds to the larger rugae or to the finer nodules present over the surfaces of the latter. Molesworth (1933) referred to papilloma formation in his material.

No Peyer's patches could be clearly distinguished in the older distal regions. Erb and Farmer (1935) report enlargement of these patches in acute cases. In such an acute case Jackman (1934) observed a firm haemorrhagic exudate and Sproull (1936) refers to a diphtheritic membrane. Despite the extensive loss of tissue in the present lesion, the surface remains surprisingly free from debris or exudate. This clean surface persists in the healed case, according to Lewisohn (1938) and an exudate is therefore no guide in identifying the extent of the lesion in the subacute or chronic stages.

Superficial ulceration has been recognised by most writers. Erdmann and Burt (1933) describe this condition as diffusely distributed, while Crohn, Ginzburg and Oppenheimer (1932) and Hadfield (1939) emphasize that the superficial ulcers are about a centimetre in diameter. The material under discussion bears this out, showing that ulceration does not necessarily supervene where epithelium has been extensively desquamated. The deeper linear ulcers occur typically

MICROPATHOLOGY

General Features:

Despite thorough analyses, no universally accepted definition of the essential histological derangement has yet been attained. Emphases of different authors seem to vary considerably. This must be due to the fact that different stages of the disease have been described by different authors, (cf. Harris, Bell & Brunn, 1933) though the present investigation has shown that all stages of the essential disorder and its sequelae may at times be recognised in material in a single suitable case of intermediate duration, provided all parts of the lesion are systematically and meticulously examined. Lesions from various situations, even the colon, (cf. James, 1938) are essentially similar.

The contention of Barbour and Stokes (1936) that the lesion has no particular anatomical arrangement, can only hold good for the very chronic cases, where destruction has advanced considerably. The present study has shown that the brunt of the microscopic disturbance falls on the submucous coat, both in regard to primary and complicating pathology. Simultaneously a reactive change appears in the adventitia; the epithelium, tunica propria and muscular layers of the intestinal wall being spared in the meanwhile. Ultimately, as Erdmann and Burt (1933) have shown, all layers are involved by oedema and infiltration. This seems to be the result of secondary complications. Unless these occur, healing can take place without any further histological elements being involved.

Primary and complicating lesions must now be clearly distinguished. While superficial ulceration, extending no further than the stratum proprium, can hardly be avoided, even in the earliest stages, its presence does not influence the picture in the deeper layers at all, as the muscularis mucosae seems to provide a very decided plane of separation between the tunica propria and submucosa in a physiological and biological sense.

as well as in terms of anatomical differences. Unless, therefore, ulceration penetrates into the submucosa, the succession of pathological states in this layer must be considered to be of a primary nature. The effects of the secondary ulceration depend largely on the stage of reorganization reached at the time the ulcer penetrates the muscularis mucosa.

Considerable difference of opinion appears among authors as to the amount of stress to be placed on various lesions recognized in their material as being primary in nature. It must be stressed once more that not sufficient care has so far been taken in distinguishing lesions of a primary character from those of a



Figure 3. General topography of the chronic lesion, showing intramural fistula and mesenteric fat. (20 x).

predominant import in the cases under consideration. Thus Hadfield (1939), in an effort to define a primary lesion in the sense of a specific histological derangement comparable to that characterizing the lesions of tuberculosis or syphilis respectively, succeeds in describing tubercle-like giant-cell follicles (which undergo characteristic developmental changes, but which are not subject to caseation, necrosis or gross destruction of surrounding tissue), which are features seen only in cases where secondary ulcerative complications have reduced the pathology in many respects to that of a non-specific chronic inflammation. These lymphoid nodule giant cell systems are never seen in the acute phase and can therefore not be primary in character.

A distinctive cellular infiltration has long been recognized as a feature especially of acute cases (Molesworth 1933). Crohn, Ginzburg and Oppenheimer (1932) originally showed that this inflammatory reaction is diffuse in the early phases and more focal in chronic cases. But the difference between the nature

of the infiltrative processes in the early and the complicated cases respectively has never been clearly defined.

Oedema has, in all descriptions, received secondary consideration, though its massive character in acute and sub-acute cases was recognized by Erb and Farmer (1935), and Mixter (1935) showed that the enormous oedema is out of all proportion to the mild cellular reaction.

The fibroblastic reaction was fully recognized by Moschcowitz and Wilensky (1927) and Jefferies (1928) as well as by Barbour and Stokes (1936), though the tendency of these latter authors to create for it a primary significance is not permissible.

While necrosis and loss of tissue is a marked feature of the secondary complications, necrosis without leucocytic infiltration has been reported in acute cases by Erb and Farmer (1935).

This mixture of tissue reactions has induced Crohn (1939) to define regional ileitis as a chronic, non-specific granulomatous inflammatory process of the terminal ileum. The sequence of events seen in the present material appears, however, to be much more distinctive and characteristic (Figs. 26 to 33).

The submucosa is affected primarily by a succession of massive oedema, lymphatic telangiectasis, round cell (plasma cell) infiltration, and fibroblastic proliferation. Unless ulceration complicates the picture, the plasma cells and their satellites or derivatives again disappear, leaving via the dilated lymphatics in a remarkably swollen or satiated condition; the lymphatics return to normal; and the continued fibroblastic hyperplasia results in the deposition of light scar tissue and ultimately complete healing. Simultaneously with these events in the submucous sheet oedema, hyperaemic, exudative, infiltrative and gross hyperplastic changes, occurring in a characteristic pattern, make their appearance in the subserosal adventitia. When, as usually happens, intramural ulceration and fistula formation supervenes, the effects of the newly invading inflammatory tissue on the primary lesions are so extensive as to modify their appearances grossly, bringing about subsidiary changes and leading to involvement of all layers of the intestine and even its mesentery.

EPITHELIUM

The gross disturbances which affect the subjacent strata are not accompanied by any conspicuous reactive changes in the intestinal epithelium itself (Fig. 4, 5). In the earlier lesions cloudy swelling and paucity of active goblet cells is seen. This epithelium is thus either injured or dormant. As Erb and Farmer (1935) have shown, a surface exudate may be present in acute cases. Pronounced subepithelial oedema of the tunica propria contributes towards the whole epithelial sheet being raised off the papillae and thus being lost. Before it is lost it appears thickened and this may correspond to the hyperplastic epithelium seen by Baird (1940) in the acute phase. Fragments may remain in the deeper reaches of the interpapillary crypts. Crohn, Ginzburg and Oppenheimer (1932) have described this

appearance as glandular destruction and epithelial atrophy. The present material shows that mechanical removal of the epithelium is the essential feature, just as a blister facilitates the loss of cuticle covering it. Moreover, widespread mitotic activity in the region of the crypts shows that attempts are being made to restore the lost epithelium which has been shed from the apices of the thickened mucosal papillae. Where submucosal repair has been effected in lesions not complicated by ulceration the epithelium returns to normal. In situations complicated by abscess formation, either no epithelium is restored or, where crypts persist, goblet cells are present in more than usual profusion. The high columnar epithelium found by Molesworth (1933)

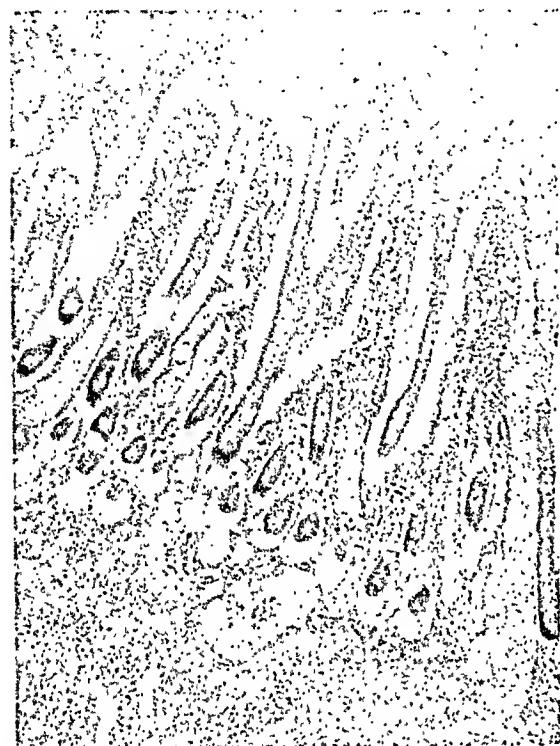


Figure 4. Oedema in the stratum proprium, with incipient epithelial desquamation in the acute lesion. (135 x).

in association with goblet cell hyperplasia (also noted by Colp, 1934) was not observed in the present material. These crypts are also more tortuous, shallower and broader and more widely spaced than in normal intestine—a feature also observed by Lewisohn (1938). No metaplasia of the epithelial cells, such as reported by Douches and Warren (1934) as a possible pre-cancerous state, was seen in this material.

TUNICA PROPRIA

No disease could demonstrate as distinctly the differences between the tunica propria and the submucosa, respectively, reflected in the separate ways they react to what is possibly the same factor influencing them simultaneously in regional ileitis. Sub-epithelial oedema has already been referred to. In the early stages this is all that may be seen in the mucosal papillae (Fig. 4). The oedema also persists somewhat longer here than in the submucosa. No cellular infiltration or other

change, except some dilatation of lymphatic loops in the apices of the papillae can be observed while the mucosa remains undamaged. Loss of the epithelium does not even influence the mucosal composition. When once the cores of the papillae themselves are damaged, a mild inflammatory reaction is set up, with polymor-

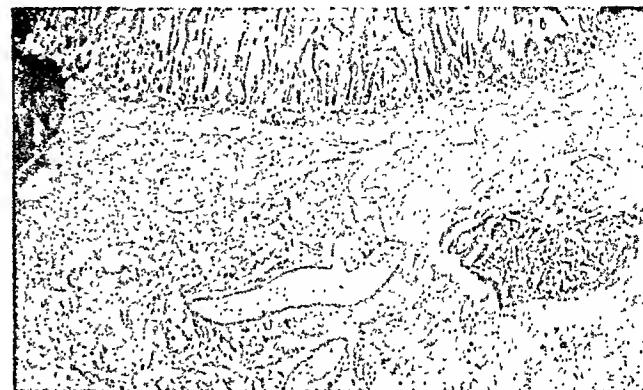


Figure 5. Lymphangiectasis, interstitial oedema and commencing round cell infiltration of the sub-mucosa of the primary lesion. (60 x).

phonuclear leucocytes and scanty fibroblasts appearing between the normal round cells of the layer (Fig. 3). This is the stage probably observed by Lewisohn (1938) who recognized eosinophil cells as well as fibroblasts. Persistence of the submucosal oedema is associated with further erosion of the tunica propria and ultimately abscess formation with its total destruction or its infiltration with leucocytes. If and where these lesions heal, the papillae temporarily remain hyperplastic, but ultimately the whole mucosa atrophies. This is a secondary effect.



Figure 6. Fibrosis, slight persistent juxta-muscular haemorrhage and sub-serosal round cell nests of the adventitia. (135 x).

SUBMUCOSA

As has already been stated, the main and earliest reactions affect the submucosa (Figs. 3 and 5). In the youngest lesion only vast interstitial oedema is observed, so that mesenteric folds become obliterated. Curiously enough, though occasional reference to this oedema has been made in the literature, the reaction has never been considered as a primary lesion, which it certainly represents. Crohn, Ginzburg and Oppenheimer (1932) referred to it as an exudative change associated with inflammation. Almost simultaneously, gross lymphatic telangiectasis appears, (Fig. 5) large distorted lymph

sinuses crossing the submucosa in all directions. Oedema and lymphatic dilatation may have a common origin, and the increased intercellular fluid may represent lymphoedema, which Hadfield (1939) regards as obstructive in type.



Figure 7. Sub-serosal collection of giant cells and spindle-shaped foreign body just beneath breach in continuity of hyaline sub-serosal sheet. (225 x).

At the next stage a diffuse round cell infiltration of the oedematous tissue follows (Fig. 5). The round cells are arranged in cords and masses or are irregularly scattered. In these early stages no tendency whatsoever towards follicle or nodule formation can be observed,

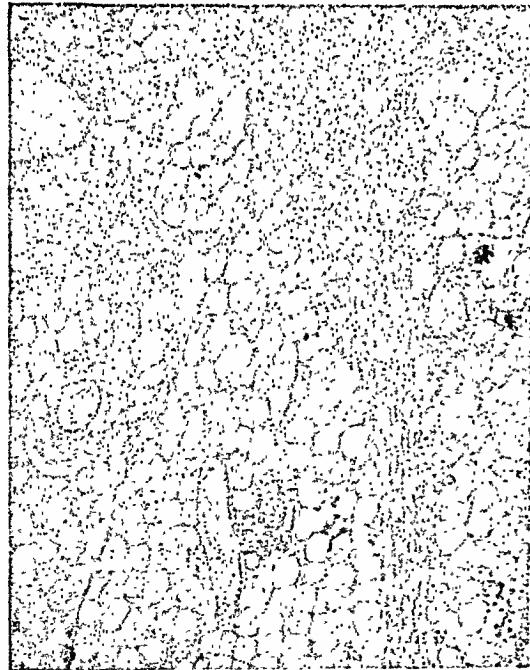


Figure 8. Fibrosis and interstitial infiltration of the juxta-intestinal mesentery. (135 x).

the infiltrated tissues being clearly distinguishable from the original scanty lymph nodes of the submucosa, which undergo no change. The dilated lymph vessels persist, and are thus rendered conspicuous by contrast with the new cellular tissue between them (Fig. 17). The invading cells are initially restricted to the sub-

mucosa and remain localized to this tissue, except where intramural abscesses with secondary infection pave the way for further extension of the invasive process, when the adventitia itself may become involved (Fig. 3).

Fibroblasts (Fig. 15) next make an appearance from amongst the round cells. By their rapid proliferation and activity an intricate reticular web is laid down in amongst the round cells and lymphatics, so that these structures appear as if suspended on this mesh (Fig. 15). Gradually the reticular tissue, which shows marked argenophil properties, increases and pari passu the round cells vanish. If no complications, such as the usual ulceration, supervene, healing takes place, the submucosa remaining thickened, as Lewisohn



Figure 9. Dilated lymphatic and round-cell infiltration round remains of a mesenteric nerve fibre. (540 x).

(1938) has also observed. Where surface ulceration has supervened, the adjacent stromal hyperplasia appears to receive an enhanced growth impetus. Consequently reticular bands grow apace and proceed to entrap small masses of round cells, so that nodules of these remain encircled in the submucosa. Their resemblance to lymph follicles is increased when endothelial elements among them, probably derived from entrapped lymph sinuses, tend to organize into central germinal centres, which, however, are not present in all nodules. These nodules correspond to the lymphoid centres, reported by Lewisohn (1938) and claimed by Hadfield (1939) as the primary lesion. They are not lymph follicles, however, as they consist of plasma cells and are accidentally formed. They may be distributed throughout the submucosa, but tend to be found nearer the muscular layers (Fig. 20).

As ulceration and fistula formation complicate the primary lesion at almost any stage in its evolution, a variety of secondary submucosal lesions may result

Ulceration brings with it a limiting wall of leucocytes and necrotic material. When these invade the submucosa and spread laterally, they invade any uninfiltrated submucosal oedematous tissue diffusely. (Fig. 3). Their presence ultimately provokes an hyperaemic zone, and then the infiltration goes more slowly. If, on the other hand, the newly invading polymorphonuclear cells of

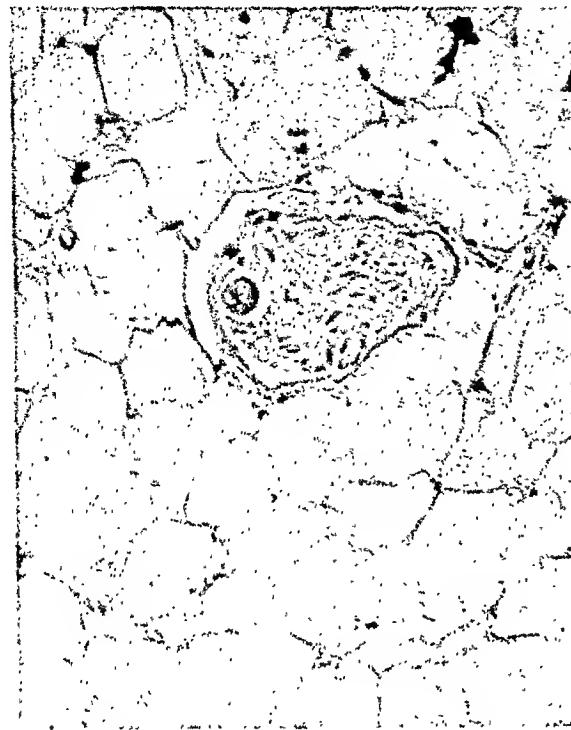


Figure 10. Swollen nerve fibre with spherical, refractile, darkly stained inclusion. (900 x).

the ulcer are brought into contact with a pre-existing round cell mass, the latter apparently recedes, for the two cell types do not mingle (Fig. 20). In such situations the new mass does not extend beyond the limits of the original mass. An exudate appears between the two masses and fibroblasts proliferate here, while fibrous tissue becomes deposited. In this intermediate zone, foreign body giant-cells may make an appearance. If the fibroblastic reaction in the primary lesion has already occurred when the new abscess reaches it, further extension of the ulceration is apparently checked. Where the fistula, in its intramural extension, penetrates vertically instead of spreading laterally, the round cell mass advances ahead of it and penetrates the muscular coats and into the adventitia. Once this has happened, there is apparently less chance of the ulceration being checked.

The contrast between the effective repair following the most extensive but uncomplicated primary infiltration of the submucosa and the progressive destruction of anatomical constituents of the bowel wall, which supervene as soon as submucosal ulceration and secondary infiltration has occurred, is a most remarkable feature of regional ileitis.

MUSCULAR COATS

It is surprising to what extent the muscularis mucosae remains intact despite gross changes in its vicinity. This

feature was originally observed by Bockus and Lee (1935) who also noted that it hypertrophies. Hypertrophy has been observed in quite the earliest lesions and persists throughout the various stages of the disease. Very little, if any, damage occurs in it at first. But when ulceration supervenes, the hypertrophied strands are involved in the infiltrative process preceding it. The layer remains intact, however, until general loss of tissue creates a hiatus also in this sheet.

The internal muscular coat undergoes the least changes in early stages. While it is still more or less normal in appearance during the primary stages of the lesion, hypertrophy of the external coat may already be seen. In the later stages even the internal layer hypertrophies, so that ultimately all muscle layers are increased in thickness, as Bockus and Lee (1935) and Hadfield (1939) have also shown, as well as the illustrations in Barrington-Ward's paper (1938). Where the lesion heals again in uncomplicated cases, muscularity returns to normal, as shown also by Lewisohn (1938).

The muscular coats are not involved by either the oedema, lymphatic dilatation and cellular infiltration of the submucosa or the hyperaemic reaction of the adventitia, in the primary disorder. When ulceration commences, however, and advances towards the muscular coats, round cell invasion, particularly towards the

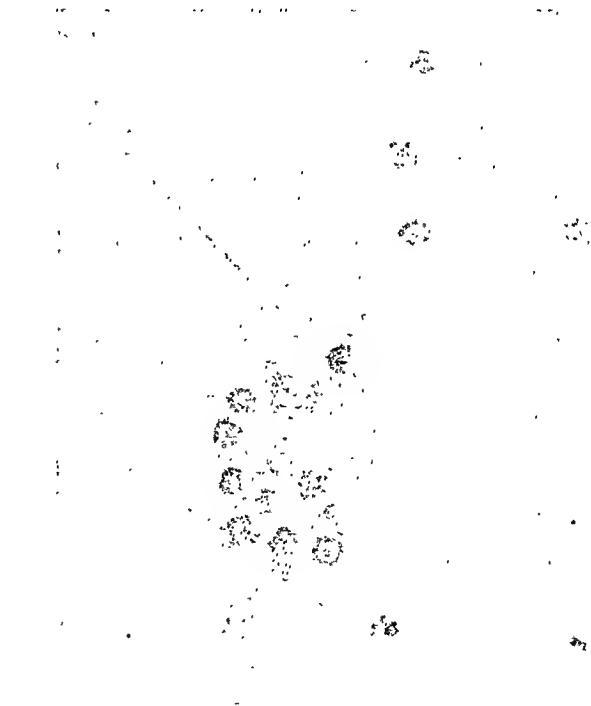


Figure 11. Interstice between fat cells choked with swollen vacuolated plasma cells. (1800 x).

mesenteric border, first occurs; dilated lymph vessels penetrate the muscularis and dilated blood capillaries pierce between its fibres, leading the way for the secondary infiltration with polymorphonuclear leucocytes, lymphocytes and eosinophil cells (also observed by Jefferies, 1928) which disrupt the continuity of the muscle layers and separate the individual fibres from one another. Damage to the actual muscle fibres does

not occur, as Erb and Farmer (1935) have observed. Almost normal, but isolated smooth muscle fibres are constituents of the later tissues bordering on the penetrating ulcer. Despite this, however, it is unlikely that this muscular layer will ever be reconstituted from these remnants, should repair become possible.

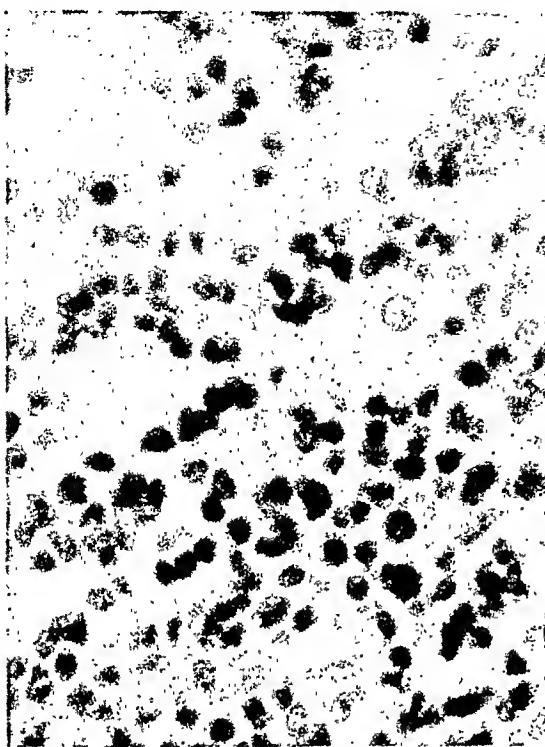


Figure 12. Varieties of round-cells invading the oedematous sub-mucosa. Note absence of supporting tissue. (1800 x).

ADVENTITIA, SEROSA AND MESENTERY

Quite the earliest reaction in the adventitial layer appears to be massive oedema and profuse hyperaemia with interstitial haemorrhage. These changes take place before any cellular infiltration makes an appearance within the layer. The vascular reaction is seen in the zone immediately superficial to the muscular coat, and the oedematous layer lies between it and the serosal layer. Similar oedema has been observed by Jefferies (1928), Bockus and Lee (1935), Jackman (1934), Erdmann and Burt (1933), though in the sections examined by the latter two authors early infiltrative changes had already appeared. Interstitial haemorrhage also characterizes acute cases (Jackman 1934). Hyperaemia has been noticed by Colp (1934) and Mailer (1938).

In older lesions relatively slight round cell infiltration takes place (Fig. 6). The contrast between the sequelae of oedema in the submucosa and oedema in the adventitia respectively was originally observed by Crohn, Ginzburg and Oppenheimer (1932). Indeed, dense infiltration only occurs opposite extensive ulceration with secondary inflammatory reactions. Instead of round cells there appears in this zone a dense avascular tissue built up from fibroblasts, cells of endothelial origin and scattered round cells, which latter lie nearest

the surface. As the lesion grows older, it becomes densely fibrotic, the round cell zone becomes narrowed to a thin sheet immediately subjacent to the serosa, and patchy degenerative changes may set in. Between the adventitia and the peritoneum a serous exudate and petechial haemorrhages may be seen. This is the stage described by Mosehowitz and Wilensky (1927) as thickening of the sub-peritoneal connective tissue. In the oldest lesions, especially those opposite deeply penetrating ulcers, four new features appear, namely: lymph follicles, giant cell nests, modification of the serosal mesothelium and invading fat.

Lewisohn (1938) has recognized both sporadic foreign body giant cells and nodular infiltration of this layer with lymphocytes. The two reactions apparently have nothing to do with one another, and appear to be a late referred reaction of mucosal ulceration, as they are not seen in regions uncomplicated by fistulae. Lymph nodules are found in juxtaposition to the muscular layer only, and the descriptions of infiltration of the serosa by Coffey (1938) and Siris (1941), correspond to this feature (Fig. 21). These isolated nodules may undergo hyaline change (Fig. 22). Giant cells are also seen here but appear to be attracted to all sites of degenerative change and may thus find their

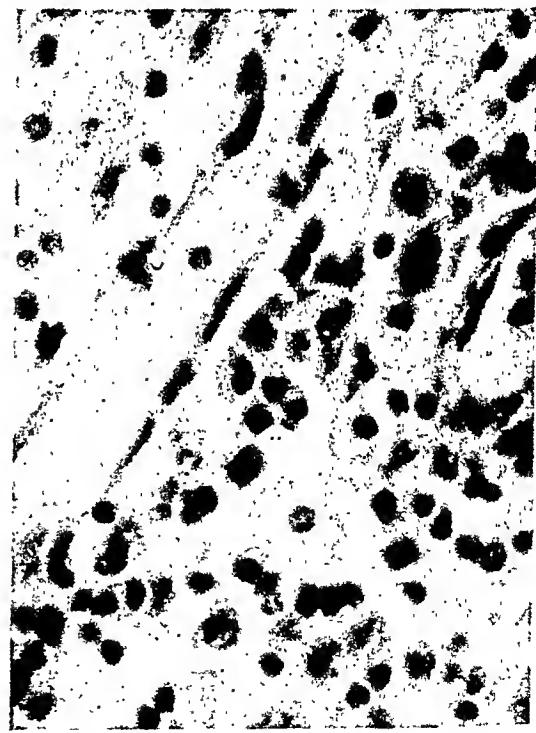


Figure 13. Plasma cells, grossly swollen and vacuolated adjacent to lymphatics; fibroblasts appearing. (1800 x).

way to the peritoneum. (Fig. 6). Near this surface they are seen to be grouped in nests with supporting endothelioid cells and abundant dilated lymph ducts. Such nests may break through the round cell zone to the serosal surface. In one case refractile spindle-shaped amorphous bodies up to 20 μ in length were seen in their vicinity (Fig. 7).

The serosal epithelium does not show much proliferative activity. The cells may swell up and may be shed, and are apparently not replaced. In a few circumscribed areas, numbers of large, frequently bi-nucleate round cells (with dense, abundant cytoplasm and large vesicular nuclei) lie in the subserosal zone. They are undoubtedly derived from serosal cells, and their presence is the

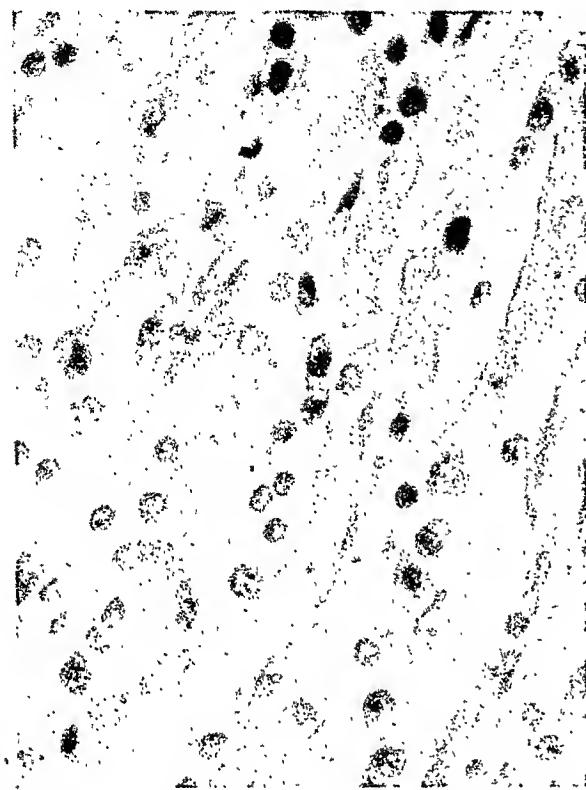


Figure 14. Later stage in round-cell infiltration of sub-mucosa. Littoral cell migrating through the endothelial wall of lymph sinus. (1800 x).

only evidence found in the direction of metaplastic changes. Where the mesothelium is lost a broad hyaline layer may replace it. Occasionally even this may be absent from the denuded area.

The invading fat is continuous with the mesentery, but may also be cut off by cicatrising bands. It tends to encircle the bowel in older lesions, penetrating between the dense sclerosing layer and the subserosal layer of round cell remnants. An excess of fat has also been referred to in the adventitia by Colp (1934). This proliferation of the fatty tissue is probably a result of low-grade inflammatory reaction in the mesentery, which is located chiefly opposite deep ulcers (Fig. 3). In these regions the mesentery is traversed by large blood vessels and dilated lymph ducts (Fig. 9) with, sometimes, cuffs of round cells. In the niches between the fat cells are to be seen round cells of all varieties, but predominantly plasma cells, either singly or in clumps (Fig. 11). Fibroblasts also appear here and eventually the mesentery is cut up by broad strands of cellular fibrous tissue (Fig. 8).

LYMPHOID TISSUE AND LYMPHATICS

Much attention has been given to the characters of lymphoid tissue in regional ileitis by Hadfield (1939)

who claimed that the primary lesion in this disease is a microscopic lymphoid nodule with a germinal centre, eight to eighteen such nodules being packed into a square centimetre of submucosa. Later the lymphoid zone disappears, the centre proliferates and forms reticulum. Giant cells then make their appearance within these centres. He also claims that non-specific lymphoid hyperplasia is present in 95% of cases. The only other authors who have reported on an increase of lymphoid tissue are Coffey (1938) who saw such follicles in the very chronic stages, and Jefferies (1928) who modified his statement by recording that polymorphonuclear leucocytes penetrate into the germ cell zones. Much depends, of course, on one's interpretation of a lymphoid follicle. Those who accept the separate identity of a plasma cell, and who regard the lymph follicle as a highly organized, stable, reticuloendothelial body, will agree that an aggregation of plasma cells and other round cells with intermingled fibrocytes cannot be regarded as a lymph follicle. In the earliest recorded detailed account of this condition by Moschcowitz and Wilensky (1927) the statement appears that the lymph follicles observed by them constituted an illusion created by the packing together of the infiltrating round cells. The present investigation confirms

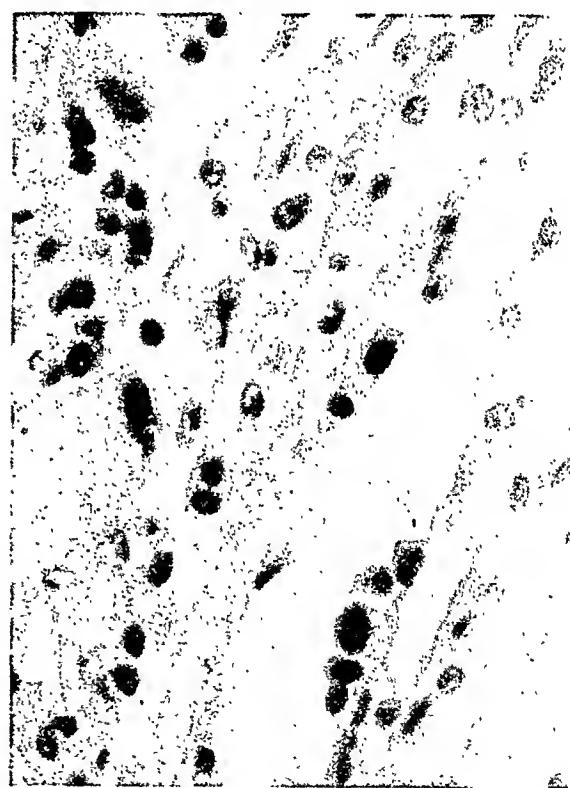


Figure 15. Healing primary submucosal lesion. More lymphocytes, fewer plasma cells. Extensive fibrocyte matrix. (1800 x).

this view fully, and the mechanism of formation of the round cell aggregates has already been sketched, when the manner of replacement of the original round cell contents of the submucosa, by means of fibroblasts and fibrous tissue, during the primary stage of the disease, was described.

The fate of the normal lymphoid tissue of the intes-

tinal wall and the appearance of these plasma cell aggregates are therefore two separate problems. The plasma cells eventually disappear as the lesion heals or as the fistula formation leads to their replacement by new inflammatory cells. Occasionally they persist, and hyaline changes may appear within them.

The true lymphoid tissue may temporarily undergo



Figure 16. Secondary polymorphonuclear infiltration without degeneration involving the partially healed primary lesion in the submucosa. (540 x).

hyperplasia; may show regressive changes or may remain unaffected. Most remarkable of the features observed in this condition is the fact that the large numbers of diffusely distributed lymphocytes of the tunica propria (probably located here as they leave the body via the intestinal tract, but just as probably subserving metabolic, endocrine and defensive purposes) and the well organized lymphoid nodules and Peyer's patches, do not undergo any serious alteration either in numbers or characters during the initial stages, when gross round cell infiltration of the submucosa is appearing. Later, when ulceration supervenes, polymorphonuclear leucocytes may appear alongside of them in increasing numbers, or some of them may degenerate.

The only sites at which hyperplasia, conglomeration and degeneration of the endothelial cells of the germinal centres have been observed, are at the bases of mucosal lymph follicles, and in the adventitia near the serosal surface or near the muscle layer, and in the mesentery adjacent to blood vessels. These changes, which correspond to Hadfield's description of the primary lesion,

are only found near extensive ulceration. Occasional giant cells are found in association with them, and they probably represent completely non-specific secondary reactions.

Dilatation of the lymphatics is a prominent feature also in the present material. This peculiarity of regional ileitis has been repeatedly recognized, originally by Erdmann and Burt (1933) and also by Mixter (1935). Erb and Farmer (1935) have shown that this telangiectasis of the lymphatics is a feature of the acute phase. This may account for the fact that it is not given prominence to in the descriptions of Crohn and Hadfield who apparently worked on much more chronic lesions. Bockus and Lee (1935) have noticed that the dilated sinuses are filled with reticulo-endothelial cells. The round cells undoubtedly originate from or leave via the lymphatics, as many of the smaller sinuses were found to display numerous littoral cells, some in the process of passing through their walls (Fig. 14). The cells of the larger sinuses were found to be of a mixed variety in the present material. These larger sinuses sometimes appeared to be choked with these cells. The observation



Figure 17. Lymphangiectasis persisting after cellular infiltration and fibrocyte formation has already commenced in the submucosa. (900 x).

of Sproull (1936) that the submucosal lymphatics are dilated up to the muscularis only appears to be true for the uncomplicated lesion. When secondary ulceration and inflammatory invasion appear, dilated vessels also vanish near the abscess but seem to follow the round cells, which, as already described, now come to lie amongst the muscle cells and in the adventitia im-

mediately adjacent to the muscle layer. (Fig. 21).

Lymph glands were not available for study in the present case, as they did not appear to be involved. Erb and Farmer (1935) mention oedema, congestion and dilated lymph ducts as the conspicuous histological lesion of the acute phase, while Hadfield (1939) has shown that giant cell systems, similar to those he



Figure 18. Argentophil, irregularly arranged, wavy fibres deposited in the submucosa as a result of healing of the primary lesion. (225 x).

described for the wall of the intestine, may occur in the lymph gland even in cases when absent from the lesion in the bowel itself. Sometimes, he records, these systems may be obscured by lymphadenitis. Their presence does not lead to fibrosis. Bowen and Fay (1939) who have examined the histological appearances of the lymphatic glands in a case dying from other causes nine years after successful ileo-colostomy are convinced that involvement of the lymphatic glands in regional ileitis is a complication of the primary lesion and have neither a causal nor essential role in the disease process.

BLOOD VESSELS

In the early lesion the typical vascular reaction is that of dilatation of the lymphatics ducts of the submucosa, and engorgement of the blood vessels of the juxta-muscular zone of the adventitia, already referred to. These blood vessels have not been observed to show any peculiarities. Endarteritis obliterans has been observed in sub-mesothelial vessels, and this endothelial proliferation is probably part of the protection aimed at in instances where relatively large vessels pierce the avascular subserosal layer to open into the peritoneal

cavity, where the serosal epithelium has been shed, or to contribute towards the sub-mesothelial haemorrhages in these regions. The perivascular collections of plasma cells and lymphocytes described by Binney (1935) probably correspond to the remnants of the round cell migrations to the juxta-muscular layers. Perilymphatic aggregations of round cells have been observed in the mesentery, however, and even lymph follicles. These may be hyperplased normal constituents. No vascular thrombi, such as described by Erb and Farmer (1935) in acute cases, were seen. This agrees with Jackman's experience. (1934).

NERVOUS TISSUE

Because nervous tissue requires special fixation for purposes of study, it is seldom easy to display in pathological material, where formalin fixation is usually resorted to. Consequently, a nervous lesion in a structure such as intestine must have attained gross proportions before being recognized. The present material was no exception, and the very presence of abnormalities of the nervous tissue, no matter how minor in appear-

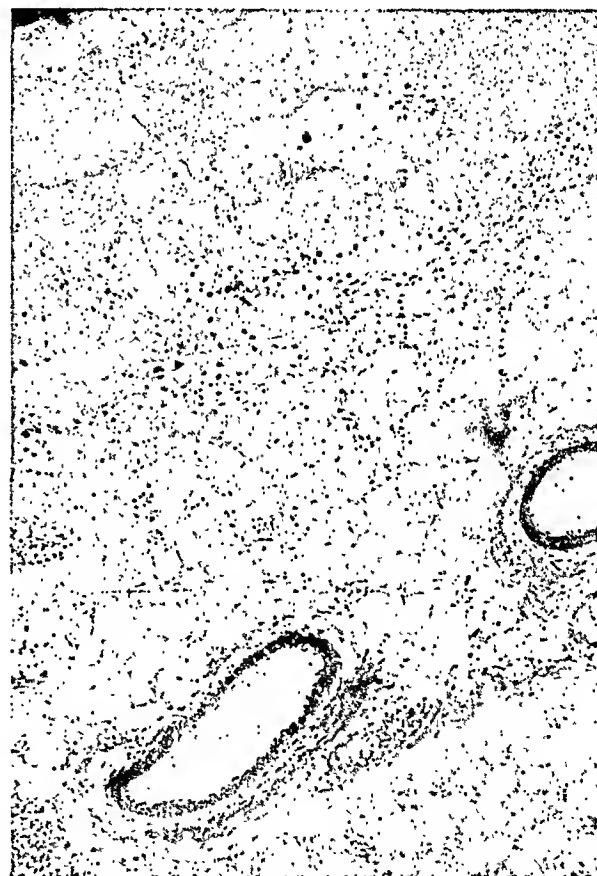


Figure 19. Argentophil properties of mast cells in the adventitia near primary lesion. (540 x).

ance, invites serious consideration. In at least one publication, reference to early involvement of Auerbach's plexus has been made (Barbour and Stokes, 1936). In the present material, round cell infiltration appears very early in the zone of Auerbach's plexus, whose component elements are difficult to distinguish and probably obscured and distorted by the presence

of the infiltrative cells. This disturbance is, by contrast with the enormous changes in the submucosa and adventitia, relatively inconspicuous; but, occurring, as it does, between two muscle layers showing no infiltrative change whatsoever, it becomes highly suspect as a site of serious disorder.

At a later stage the massive cells may readily be

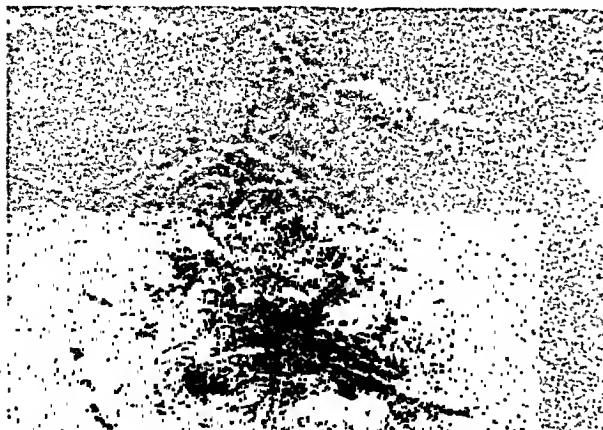


Figure 20. Zone of junction between the secondary abscess wall of cells and the partly healed primary lesion. Giant cells present here. (225 x).

demonstrated along the mesenteric border in this intermuscular plane. They show a considerable quantity of intensely staining cytoplasm. These cells are either giant macrophages derived from the sheath elements of the nervous plexuses, or are hypertrophied abnormal ganglion cells. They cannot be confused with ordinary Langhans or Dorothy-Reed giant cells, though giant cells in this situation have been referred to by Barbour and Stokes (1936) as foreign body giant



Figure 21. Aggregations of plasma cells in follicle-like arrangement in the juxta-muscular, fibrosing adventitia. Note lymph sinuses passing through muscularis. (225 x).

cells. Such true Langhans cells do occur at the latest stages (Fig. 23). Examination of the adventitia and mesentery reveals that the nerves leading towards the bowel wall are distinctly swollen. Spherical, deeply staining, highly refractile bodies have been observed in such nerve bundles (Fig. 10). These bodies measure about 15 μ in diameter. Their identity cannot be estab-

lished. These turgid nerves are ensheathed in fat cells. At first there are no signs of infiltration in their vicinity; but foreign body giant cells and endothelial cells are observable round degenerating nerve bundles near the muscular coats in the older lesions (Fig. 9). No components of Meissner's plexus could be differentiated.

CYTOLogy

Considerable confusion still exists in the literature about the predominant cell types which characterize the primary lesion. This is undoubtedly due, chiefly, to the fact that such material as has been described by different authors represented different stages in the evolution of the pathological processes. On the other hand, some confusion is evident with regard to the interpretation of the dominant cell types found in these cases, and the unstable terminology of reticulo-endothelial derivatives.

The round cells seen most abundantly in some early lesions have been referred to variously as: mononuclear cells or phagocytes (Mock, 1931; Colp, 1934; Sproull,

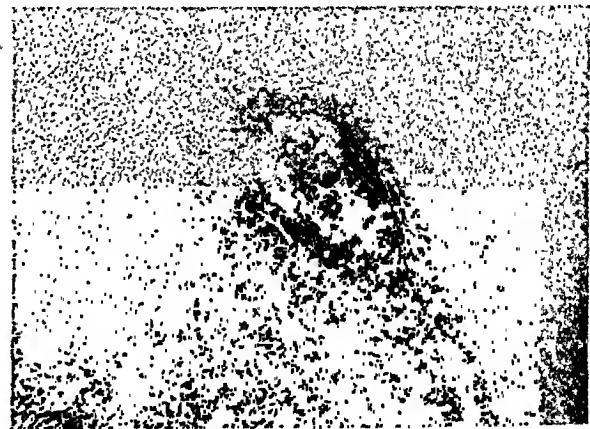


Figure 22. Hyaline change in the plasma cell unit at the stage of healing of the adventitial lesion. (225 x).

1936), histiocytes (Meyer and Rosi, 1936), endothelial leucocytes (Erb and Farmer, 1938; Bockus and Lee, 1935). The descriptions of these cells agree so closely that they must be regarded as identical cells. The next cell type seen in these lesions is the plasma cell, recognized by Erdmann and Burt (1933), Mixter (1935), Sproull (1936), Barbour and Stokes (1936). The majority of lymphocytes reported by other authors are probably also plasma cells, as many still confuse the two.

The present investigation has shown that all these round cell types probably have a common origin. The monophyletic view of reticulo-endothelial cell origin provides an adequate explanation for their presence. Those who believe with Maximow that plasma cells, histiocytes and blood mononuclear cells can be converted into macrophage polyblasts in pathological tissue, will recognize the significance of the primary lesion in the submucosa. In the present material all shades of transition from the typical plasma cell to the macrophage polyblasts can be traced. (Figs. 12 to 15). With so many plasma cells in the tissue, it is not necessary to

search for pure endothelial cells or for histiocytes to explain the other round cell types. The plasma cells further show a great range of variation. Some possess pyknotic nuclei; others vesicular nuclei,—probably old and young forms respectively. Bi-nucleosis is quite common, probably representing stages in the rapid mitotic proliferation of the plasma cells rather than stable types. In some of these binucleates one nucleus is pyknotic. Vacuolation, commencing immediately adjacent to the nuclei, is seen in various stages of satiety. Many of the plasma cells increase to about four times the ordinary diameter as the result of the presence of these vacuoles. These latter cells tend to be found near lymph sinuses. Plasma cells also line the endothelial surfaces of the lymph ducts and may be identical with the so-called endothelial littoral cells described by Hadfield (1939). Sproull (1936) observed a serosal lymphatic completely plugged with large mononuclear cells showing a foamy, lipoid-filled cytoplasm. Similar observa-



Figure 23. Giant cell group between the muscular sheets. No nervous elements or neurogenic macrophage distinguishable in this late lesion. (540 x).

tions were made in the present material in the mesentery, though the contents of the vacuoles were not found to be doubly refractile, in spite of resembling lipoids, when looked at with the polariscope. (Figs. 19 to 24).

Lymphocytes were also present, but in very small numbers only and at a later stage (Fig. 15).

The next cell type which has attracted attention in some acute cases is the mast cell. These have been reported by Mock (1931), Erdmann and Burt (1933) and Binney (1935). They are not as numerous as the foregoing cell types, but form such a distinctive element of the early lesion of regional ileitis, that their presence merits some comment. Recognized by their distinctive nuclei and metachromatic, argentophil, coarse, cytoplasmic granules, they are inseparably intermingled with the round cell mass of the submucosa. They do not, however, enter lymph sinuses, as do the other cells. They are probably produced by the activation of the normal mast cell constituents of the submucosa, when oedema appears, for they may be present in increased

numbers when the remainder of the infiltrating cell mass is still absent.

In the later stages of the primary uncomplicated lesion, and also in the granulating walls of the second-



Figure 24. Typical argentophil granules in a mast cell of the submucosa. (1800 x).

ary abscesses, fibroblasts and fibrocytes in all stages of cytological organization may be observed. They were originally seen by Mock (1941) and have since been recognized by most observers.

Polymorphonuclear leucocytes do not take part in the primary invasion. Erb and Farmer (1935) saw none, and Mixter's contention that they are present only at the ulcers, holds good for the present material as well. They compose the walls of the invading ulcer, (Figs. 16 and 17). Polymorphonuclear leucocytes are, however, more readily seen in the mucosa, where numerous eosinophil cells also make an early appearance. These latter are seen in the submucosa only, as a late result of healing of lesions created by the ulcers, and are therefore usually found in association with fibroblasts, as was also observed by Erdmann and Burt (1933), and Lewisolin (1938).

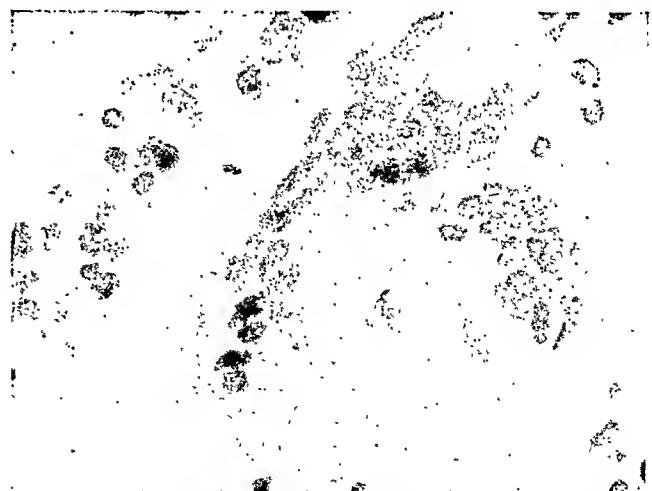


Figure 25. Giant cell found in the adventitia. Note the refractile granules. (1800 x).

Much prominence has been given in previous descriptions to the presence of multi-nucleate giant cells in lesions of regional ileitis. Only Langhans (foreign body) cells have been seen and no mention has been

made of Dorothy Reed cells. Colp (1934) maintains that those he saw were not of the Langhans type. With few exceptions (Bockus and Lee, 1935) they have been reported by all authors. Hadfield (1939) found them present in 65% of cases only, suggesting that they may undergo natural regression or may be absent from the bowel wall, but present in the regional lymph glands.

No clarity exists as to when they first make an appearance. Harris, Bell and Brunn (1933) contend

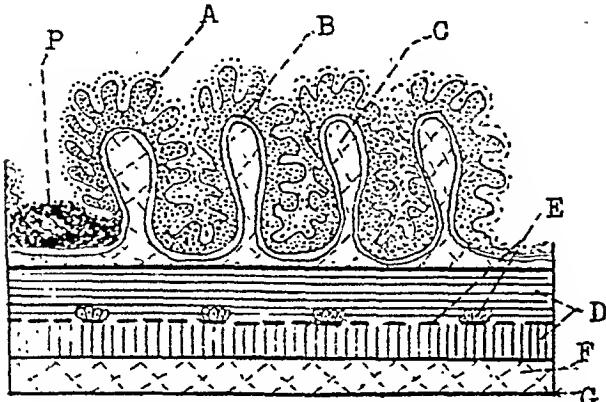


Figure 26. Normal terminal ileum, longitudinally sectioned.
 (a) Lamina propria and villi covered with epithelium.
 (b) Muscularis mucosae.
 (c) Submucosa and transverse folds.
 (d) Internal and external muscular coats.
 (e) Auerbach's plexus.
 (f) Adventitia.
 (g) Mesothelium of serosa.
 (p) Peyer's patch.

Lewisohn (1938) found them in a healed case. On the other hand, Barbour and Stokes (1936) state that they are restricted to the intermuscular plane in juxtaposition to Auerbach's plexus. As has already been pointed out some of the large cells are probably either hypertrophied, injured, ganglion cells, or else may represent giant cell macrophages, originating in the cells of Schwann, as may occur elsewhere in the body. Similar cells have been described in the present mater-

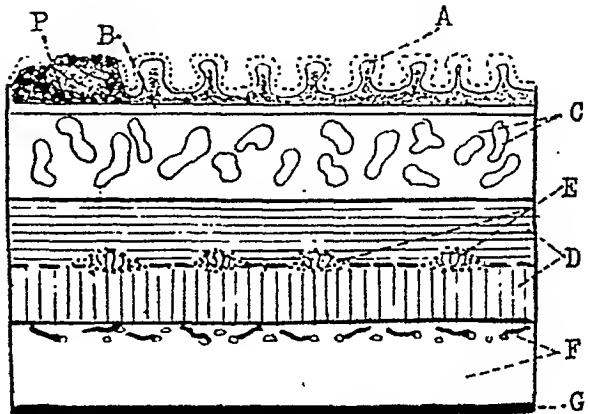


Figure 27. First phase of primary lesion. Note:
 (a) Oedema of lamina propria blunting villi.
 (b) Straightened out muscularis mucosae.
 (c) Oedema, dilated lymphatic vessels (?) paralysed and absence of transverse folds of submucosa.
 (e) Changes at Auerbach's plexus.
 (f) Juxta-muscular hyperaemia and subserosal oedema.

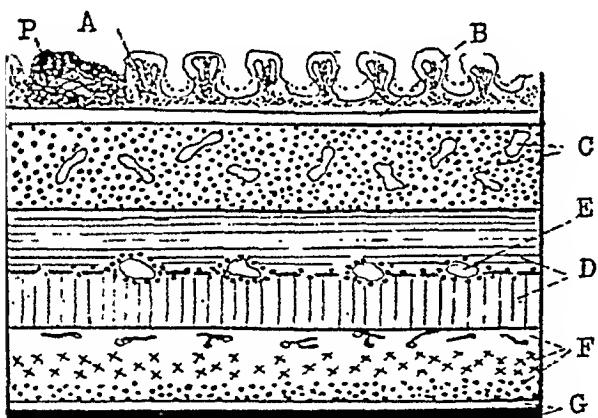


Figure 28. Second phase of primary lesion.. Note:
 (a) Desquamation of epithelium of villi and dilatation of lymphatics in villi.
 (b) Hypertrophy of muscularis mucosae.
 (c) Round-cell infiltration of submucosa.
 (e) Hypertrophy of muscular sheet.
 (f) Subserosal round-cell infiltration.
 (g) Thickening of serosa.

that they are a feature of the third or stenotic, (cicatrizing) stage of the disease, and Binney (1935) associates them with the ulcers. Neither Jackman (1934) nor Erb and Farmer (1935) who gave detailed accounts of acute cases, report the presence of these cells, so that they may be presumed not to make an appearance before the condition has reached the subacute or chronic stage. The present study confirms this view.

Similar ignorance persists about their precise localization. Colp (1934) stated that they are present in the subserosa only, and this is the only situation in which

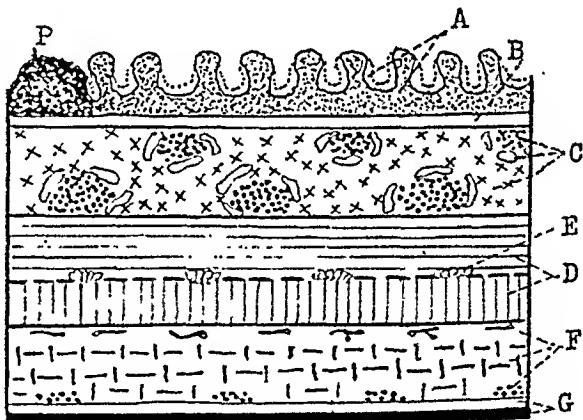


Figure 29. Third phase of primary lesion. Note:
 (c) Fibroblastic proliferation cutting up the round-cell mass in submucosa into small follicle-like masses.
 (d) Lymphatic telangiectasis passing off.
 (d) Lesions in Auerbach's plexus healing.
 (f) Fibrosis in the adventitia and hyperaemia diminishing.

ial. Later, true Langhans cells may replace them (Fig. 23).

The present study shows that, apart from the above doubtful instances, multi-nucleated giant cells may be seen in three situations, in the subacute phase of the disorder. Giant cells, often closely resembling Dorothy Reed cells, may be seen in the subserosal tissue, where some attempt at "tubercle" organization seems to be made (Figs. 6 & 7). Here they are related to the presence of degenerating endothelial-like cells, foreign bodies, organizing exudate and extravasated blood. Langhans giant cells, again, are found near degener-

ating nerve fibres in the mesentery near the muscularis. (Fig. 25). But in the great majority of instances the foreign body giant cells form a constituent of the zone of fibroblastic exudative reaction between the original round cell tissue of the submucosa and the polymorphonuclear leucocytes of the invading ulcer wall (Fig. 20).

Jellen (1937) and Hadfield (1939) claimed a decided tubercle-like arrangement for these giant cells. Such an

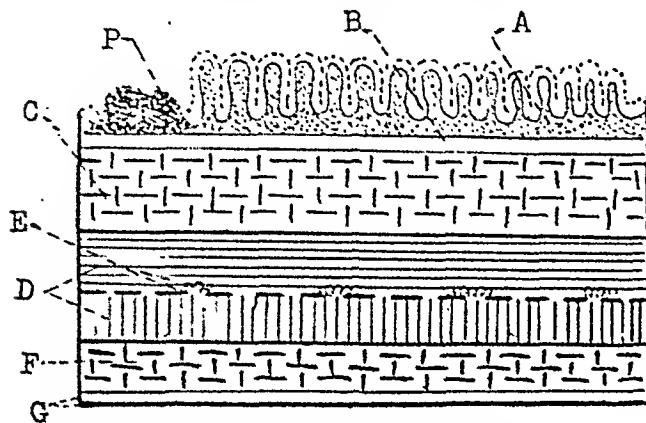


Figure 30. Healing of primary lesion. Note:
 (a) Reconstitution of villi.
 (b) Muscularis mucosa remains straight but less hypertrophic.
 (c) Light fibrosis of submucosa. No transverse folds appearing.
 (d) Auerbach's plexus normal.
 (e) Muscular coats still hypertrophic.
 (f) Fibrosis of adventitia.
 (g) Mesothelium normal.

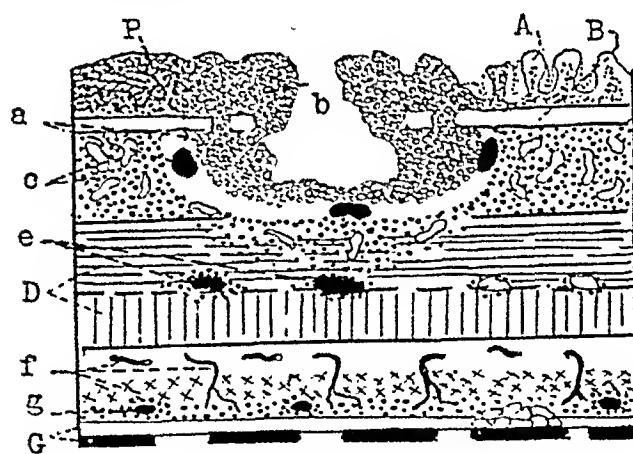


Figure 32. Secondary ulceration involving the submucosa, superimposed on second phase of primary lesion. Note:
 (a) Exudative zone containing giant-cells separating invading polymorphonuclear leucocytes.
 (b) Original round-cell mass.
 (c) Muscularis being invaded by round-cells and lymphatics.
 (d) Giant-cell changes at Auerbach's plexus.
 (e) Reactive vascular changes and giant-cell nests in serosa.

arrangement has not been commented on by other authors, and is not constantly seen in the present material. Crohn, Ginzburg and Oppenheimer (1932) also observed this, and suggested that the presence of any complex of surrounding pale cells is a reaction to the inclusion of vegetable matter.

Many authors, with the exception of Sproull, (1936), have reported various inclusions in these giant cells. Moschcowitz and Wilensky (1927) originally reported clear oval spaces only; Erdmann and Burt (1933) mentioned variously shaped, glazed, colourless particles;

Homans and Hass (1933) saw crystalline bodies, probably of lipoid origin; Binney (1935) reported vegetable and crystalline material; Barbour and Stokes (1936) found hard crystalline bodies of variable shape and indeterminate origin; Meyer and Rosi (1936) noticed vegetable fibres; Coffey (1938) crystalline matter or lipoid, probably food remnants. In the present material they were either quite empty or showed refractile vacuoles and granules (Figs. 23-25). Their

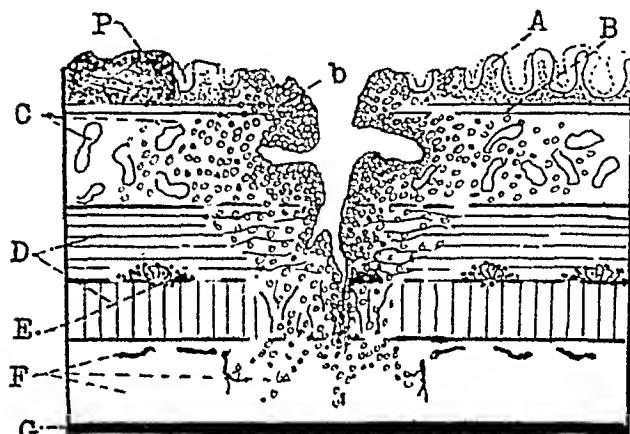


Figure 31. Secondary ulceration of mucosa superimposed on first phase of primary lesion. Note: Tendency to early perforation and diffuse infiltration of oedematous zone with neutrophil polymorphonuclear leucocytes.

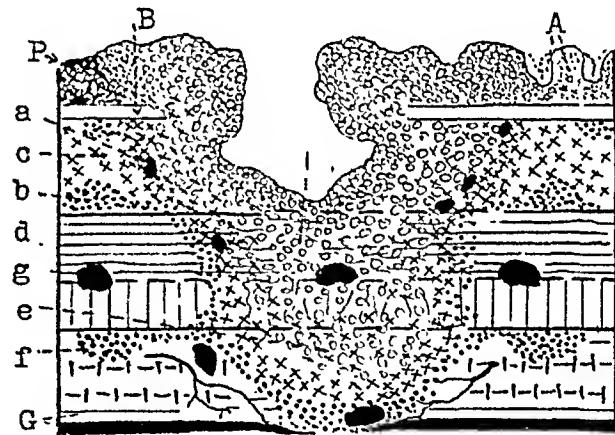


Figure 33. Secondary ulceration superimposed on fibrosing primary lesion. Note:
 (a) Giant-cell zone in submucosa.
 (b) Plasma-cell aggregates.
 (c) Fibrosing submucosa.
 (d) Muscularis invaded and disrupted.
 (e) Abscess cells penetrating into serosa.
 (f) Round-cell nests in the juxta-muscular zone.
 (g) Giant-cell scavengers in vicinity of Auerbach's plexus.

significance, other than being scavengers for material which cannot be dissolved away, has not been fathomed. Binney (1935) suggests that they may be responsible for hyperplastic fibrosis, but this view could not be confirmed. The possibility that they may be responsible for dealing with certain lipoids must be entertained, though the presence of this lipoid has not been demonstrated satisfactorily. It must be recalled that Doan, Sabin and Fortenes (1930) showed that certain portions of the lipoid fractions of tuberculosis bacilli provoke giant cell systems under experimental conditions.

MICRO-ORGANISMS AND INCLUSION BODIES

Careful search has failed absolutely to reveal any recognizable pathogenic agents. Widely scattered, extremely minute, highly refractile, rod-shaped bodies have been observed in the tunica propria, but give no bacterial staining reactions. The much larger spindle-shaped bodies in the sub-peritoneal giant cell nest, and the highly refractile spherical bodies in the mesenteric nerve fibres, mentioned before, are the only "foreign bodies" which may be recognized in this tissue. For the magnitude of the lesions observed, this apparent absence of visible biological or physico-chemical pathogenic agent is most surprising and very characteristic of regional ileitis.

DISCUSSION

The majority of the features of regional ileitis as a clinical and pathological entity, can, as shown above, be explained on a rational basis. It is, therefore, the more exasperating that the aetiology of this extraordinary condition should remain a complete mystery. To find a solution to this problem should therefore be the aim of all those who are fortunate enough to meet with cases of this disease and who have the necessary facilities to undertake a serious investigation. However, due credit must be given to all those workers who have built up our information on the subject bit by bit. Through their work we are at least certain of some of the possible factors which *do not* play a direct part in the aetiology of the condition. It would seem advisable in these studies to approach the subject in the widest possible manner.

Consideration of the epidemiology of the disease provides very little evidence about possible aetiological factors. Perhaps too little has been done in this direction. If young males from all over the world are more frequently affected than females some endocrine factor may contribute towards the aetiology. The sporadic character of the disease also suggests that an infective aetiology is improbable, but not excluded.

Features of the clinical history afford very little guidance. The contrast between the tendency for acute cases to undergo spontaneous cure more frequently than to pass over to the chronic stage, and the change in the character of the disease once it has become chronic, chief of which being that spontaneous cure is then no longer probable, focuses attention on the difference in pathogenesis of the two phases. The chronic stage might be regarded as a complication of or a sequel to the acute lesion, rather than being a logical elaboration of the original uncomplicated lesion. It is possibly of an inflammatory (though not necessarily infective) character. That its course is inescapably influenced by the nature of the primary lesion is set forth below. The recurrence of the disease after surgical excision of the original lesion is a pointer with regard to the aetiology. Where the disease has recurred owing to inadequate resection or owing to "skip areas" having been overlooked at the time of operation, no new fact

is contributed. But when it is absolutely certain that radical excision had been effected and the disease reappears at a later stage, one is bound to conclude that either the aetiological factor persists in the patient or his environment, that the disease selects certain individuals particularly prone to it, and that this susceptibility persists after operation, or that the original disorder brings about changes in the body systems, which facilitate the re-appearance of the relatively non-specific chronic lesions at a later stage: for it is true that acute lesions have never been reported in recurrences. It was shown by Ginzburg and Garlock (1942) that post-operative diarrhoea, a frequent complication, is not due to persistence of the original lesion in an unrecognizable form, but due to the increased fluid which reaches the large bowel when portions of the ileum are resected or short-circuited. Their experience that the patient's condition may improve and the chronic lesion heal when ileo-colostomy with exclusion, but no resection, is performed, has a most important bearing on the aetiology in so far as it shows that no causative agent is inherent in the lesion itself, but that its persistence is due to the lytic influence of the intestinal fluid on the ulcers or fistulae. That this intestinal fluid is not itself abnormal is suggested by the fact that no erosion of the incised surfaces of the bowel, where operative repair has been introduced, has been reported.

The contributions of clinical pathology have all been negative, no clue being found which might lead to the discovery of a pathogenic agent. Nor has any evidence been found to show that the body adjusts itself in a peculiar manner to the disease process. The studies have, however, been admittedly few and incomplete. Nor have the few biochemical investigations already carried out produced evidence of any systemic derangement or peculiar biochemical or biophysical feature of the disease. With so many contributions suggesting the presence of lipoids and crystalline particles in the lesions, a fuller investigation of the lipid metabolism of these patients is urgently required. Such intensified biochemical and clinical pathological studies would perhaps also assist in identifying an underlying systemic or endocrine disease, which may be missed by clinical examinations.

The contribution of microbiology is much greater, but also negative. It is indeed very surprising that the lesions were consistently sterile, when contamination with faecal matter had been excluded, if one takes into consideration the "septic" surroundings of the involved segments. *It is even a matter for suspicion that no secondary infection rapidly destroys the patient.* This feature suggests that a study of the comparative pathogenic flora of the intestinal contents itself would reveal diminution of the infectivity of the fluid in the more chronic cases. No satisfactory contribution has been made on the microbiology of the acute lesions, such as that described by Mailer (1938). An infective agent may nevertheless be present at the acute stage, though the study of chronic lesions may be sterile. Sufficient work has not been done to isolate or identify or exclude mycotic agents or possible filter-passing viruses. The

progression, distribution and characters of the secondary chronic lesions are much like those round the spreading mycelium of fungal lesions; and the early acute reaction resembles the manifestations of certain virus diseases.

The most important evidence about aetiological factors must, for a long time to come, emerge from a study of the pathological anatomy of the disorder. In the present study an attempt has been made to give a comprehensive picture of the whole pathology as seen in the examined material and as reconstituted from facts culled from the large number of published papers. Particular attention has been given to the distinctive features of the micropathology of the acute and chronic lesions respectively. That the latter is a type of granuloma with a slowly developing inflammatory ulcer gaining on coincident efforts at repair, has been mentioned. Its perforating character is important for consideration at the present stage. It may safely be questioned whether the acute lesion, with its pathognomonic anatomical distribution of oedema, lymphatic dilatation and hyperaemia, and subsequent characteristic round cell infiltration and fibrosis can be regarded as an inflammatory reaction. While oedema accompanies acute inflammation, excessive lymphangiectasis does not. Hyperaemia would be more usual; but then it would be near the site of the oedema and the probable source of inflammation and not restricted to a narrow zone external to the muscular coat. The simultaneous involvement of the submucosa and serosa is also against an inflammatory reaction. Moreover, plasma cells do not usually do duty in acute inflammations. They have different phagocytic functions and are more likely to migrate in response to chemotropic than to inflammatory stimuli.

How then must one interpret this acute lesion? The theory of lymphatic obstruction has been advanced, but has found few supporters. Much more experimental work, like that done by Reichert and Mathes, is required, and fuller studies of the pathological anatomy of the lymphatic system in Crohn's disease is necessary, before a lymphangiopathy can be considered as a primary mechanism, or be rejected. Similarly, when it is suggested that the primary lesion may be due to derangement of the blood supply, detailed study of the vascular patterns in these lesions are lacking, and should be urgently examined. Fuller study of nerve anatomy and pathology are also required.

By analogy with similar lesions elsewhere in the body, the features of acute regional ileitis may be described as in the first instance acute, anatomically localized vesiculation of the bowel wall. Examination of the chief causes of such blistering is found to be due to *virus disease*; (e.g. small-pox or chicken-pox); *allergy*, especially food allergies; *chemical and physical irritation* (such as chafing, sunburn, croton oil, mustard gas, etc.) and *neuropathy* (such as involvement of the Gasserian or spinal ganglia in herpes zoster).

Virus and allergic reactions usually produce multiple lesions, though they may on occasion display regional

characters. We cannot yet exclude the former. Absence of eosinophilia is important but not conclusive evidence against the latter. Irritants cannot yet be excluded completely. We eat so many artificial and unnatural foods now-a-days and consume such varieties of medicines that a potential irritant, if ingested, may find itself digested to an irritant, absorbable composition at some stage or other in its passage through the alimentary tract. Such an agent may even be an ingredient of the daily diet, ordinarily disposed of satisfactorily. In this connection lipoids or mineral oils are most suspect, as lipid-like material has been observed in the giant cells, though no one has yet proved that these vacuoles and crystalline bodies are definitely fatty in character. The fact that "lipoids" tend to occur in macrophages in other granulomata suggests that the foreign material is a contaminant, or results from tissue destruction and has no significance from the etiological point of view.

The evidence for a neuropathic aetiology is much stronger than for any other type of mechanism, despite the apparent absence of gross lesions in the nervous tissue. But this latter concept is due to our ignorance of the degree to which nervous tissue is involved in the primary stages. The present investigation has fully convinced the author that Auerbach's and Meissner's plexuses and the mesenteric nerves are seriously affected in the early stage of the disease. Some day a primary lesion, (comparable to that affecting the spinal ganglia in herpes zoster, will probably be found in the cells of the group mesenteric ganglia or even in the parts of the coeliac plexus itself.

Simultaneous involvement of the serosa by oedema and juxta-muscular hyperaemia and of the submucosa by oedema and gross telangiectasis of the lymphatics, while other parts of the bowel wall escape, suggests that the lesion is neurogenic, for such an explanation is the only one which would account for the above features, as the dendritis of the cells in Auerbach's and Meissner's plexuses constitute the only common connection for all these elements. The terminal ileum is also the region where vagal innervation ceases and sacral para-sympathetic supply commences, and is therefore by analogy as other neuropathic disorders at transition zones, a not unlikely site for initial disorders. The segmental character, and the presence of "skip areas" are well explained on the basis of involvement of central mesenteric ganglia. If central lymphatic obstruction were the cause, collateral anastomoses would lead to less clear definition of the region affected. Extension of the collateral lymphatic circulation should also favour gradual shrinking of the lesion. New nerve connections can, on the other hand, not be built up once they are destroyed. If the destruction proceeds apace centrally, the lesion in the bowel wall will grow or "skip areas" will become involved. Progression centrally would also account for recurrences after careful eradication of intestinal lesions.

It seems possible to explain the oedema by analogy with the blistering of herpes zoster. Its persistence is favoured by paralysis of the lymphatics and blood vessels of the submucosa and serosa, respectively when

Meissner's plexus or its central connections are injured or irritated. The advent of the plasma cells must be the body's attempt at having this oedema disposed of. Plasma cells in such large numbers could carry off vast collections of lymph. The proliferation of the fibroblasts may be explained on a teleological basis, but may also be due to the growth stimulus provided when they are liberated from nervous control and placed in a favourable culture medium.

The muscular hypertrophies may or may not be related to changes in their innervation.

One may presume that if the ganglion cells are initially not seriously injured, they may soon recover. Re-institution of normal innervation will then speed up healing in the lesion, probably even when ulceration has already commenced. If nerve lesions were complete, the bowel will remain exposed to risk of further injury and chronic lesions will continue. Such absolute chronicity of lesions, with tendency to destruction of tissue, is quite characteristic of lesions within denervated tissues. No primary lytic action of intestinal juice or foreign agents need be invoked to explain slowly perforating ulcers, when we have such outstanding examples of perforating ulcers occurring in tissues devitalized by loss of their nerve supply, as occurs in the late stages of syphilis, diabetes mellitus and leprosy.

The unfailing logic of these facts impels one to accept the neuropathic theory as the most probable aetiological factor. There are many causes for neuropathy; but hardly any further search need be made than for the same sort of virus factor as that causing herpes zoster or, as recent correlations suggest, (Garland, 1943), regional varicella. *Regional ileitis may even represent a visceral form of herpes zoster.*

CONCLUSIONS

1. The literature on Regional Ileitis as a clinico-pathological entity is reviewed and suggestions made as to what is required from future research.
2. A detailed study of the pathology, particularly the pathological histology is involved.
3. The disease has two components; namely:
 - (A) *A primary phase*, characterized by
 - (i) a stage of oedema of the submucosa and serosa with dilatation of submucosal lymphatics and hyperaemia of juxta-muscular adventitial blood vessels;
 - (ii) *a stage of plasma cell infiltration* of the submucosa and serosa;
 - (iii) *diffuse fibrosis*, with disappearance of the plasma cells, except where trapped; and
 - (iv) healing.
 - (B) *A secondary phase*, characterized by ulceration superimposed on any of these phases of the primary lesion, with corresponding modification of the pathological process. There are tendencies to early or late perforation; fistulation, and granuloma formation.
4. A critical analysis of possible aetiological factors suggests that the primary disturbance is due to either acute injury of the bowel wall by a metabolite, probably lipoid in character, or results from a neuropathic disturbance involving Auerbach's and, or, Meissner's plexuses, or mesenteric and coeliac ganglia. In nature the original neuropathic lesion is possibly a type of visceral herpes zoster. It is suggested that the chronic type of secondary ulceration only occurs when ganglionic lesions are not only irritative but destructive, and thus lead to denervation of the affected bowel wall.

BIBLIOGRAPHY

- Baird, L. W., 1940. *Texas State J. Med.*, 35, 760.
 Barbour, R. F. & Stokes, A. B., 1936. *Lancet*, i, 299.
 Barrington-Ward, L., 1938. *Brit. J. Surg.*, 25, 520.
 Binney, H., 1935. *Ann. Surg.*, 102, 695.
 Bockus, H. L. & Lee, W. E., 1935. *Ann. Surg.*, 102, 412.
 Bowen, W. H. & Day, T. D., 1939. *Guy's Hosp. Rep.*, 89.
 Brown, P. W. & Donald, C. J., 1942. *Amer. J. Digest. Dis.*, 9, 70, 87.
 Chapin, W. A. R. & Crohn, B. B., 1939. *Surg., Gynec. & Obst.*, 68, 314.
 Clute, H. M., 1933. *Surg. Clin. N. Am.*, 13, 561.
 Colp, R., 1934. *Surg. Clin. N. Am.*, 14, 443.
 Crohn, B. B., Ginzburg, L. & Oppenheimer, G. D., 1932. *J. Am. Med. Ass.*, 99, 1323.
 Crohn, B. B., 1939. *Surg., Gynec. & Obst.*, 68, 314.
 Dalzier, T. H., 1913. *Brit. J. Surg.*, 2, 1068.
 Dean, Sabin, P., & Fortenes, 1930. *J. Exp. Med.*, 5, 89.
 Douches, J. C. & Warren, S., 1934. *Arch. Path.*, 18, 22.
 Erb, I. H. & Farmer, A. W., 1935. *Surg., Gynec. & Obst.*, 61, 6.
 Erdmann, J. F. & Burt, C. V., 1933. *Surg., Gynec. & Obst.*, 57, 71.
 Ginzburg, L. & Garleck, J. H., 1942. *Ann. Surg.*, 116, 905.
 Garland, J., 1943. *New Engl. J. Med.*, 228, 336.
 Hadfield, G., 1939. *Lancet*, ii, 773.
 Harji, F. L., Bell, G. H. & Brunn, H., 1933. *Surg., Gynec. & Obst.*, 57, 637.
 Hermans, J. & Haas, G., 1933. *New Engl. J. Med.*, 209, 1315.
 Hurst, A. F. & Lintott, G. A. M., 1939. *Br. Encycl. Med. Pract.*, 3, 508.
 Jackman, W. A., 1934. *Brit. J. Surg.*, 22, 27.
 Jackson, A. S., 1937. *Surg., Gynec. & Obst.*, 65, 1.
 James, I. G. I., 1938. *Brit. J. Surg.*, 25, 511.
 Jeffries, J. F., 1928. *J. M. A. South Africa*, 2, 184.
 Jellen, J., 1937. *Am. J. Roentgenol.*, 37, 190.
 Kantor, J. L., 1934. *J. Am. Med. Ass.*, 103, 2016.
 Lewisohn, R., 1938. *Surg., Gynec. & Obst.*, 66, 215.
 Mailer, R., 1938. *Brit. J. Surg.*, 25, 517.
 Meyer, K. A. & Rosi, P. A., 1936. *Surg., Gynec. & Obst.*, 62, 977.
 Mixter, C. G., 1935. *Ann. Surg.*, 102, 674.
 Mock, H. F., 1931. *Surg., Gynec. & Obst.*, 52, 672.
 Molesworth, H. W. L., 1933. *Brit. J. Surg.*, 21, 370.
 Moschowitz, E. & Wilensky, A. C., 1927. *Am. J. Med. Sci.*, 173, 374.
 Moschowitz, E., 1940. *J. Mt. Sinai Hosp.*, 7, 77.
 Pumphrey, R. E., 1938. *Proc. Staff Meet. Mayo Clin.*, 13, 553.
 Ralphs, F. G., 1938. *Brit. J. Surg.*, 25, 523.
 Reichert, M. L. & Mathes, M. E., 1936. *Ann. Surg.*, 103, 601.
 Sailer, S. & McGann, R. J., 1942. *Am. J. Digest. Dis.*, 9, 55.
 Schapiro, S., 1934. *J. Mt. Sinai Hosp.*, 1, 121.
 Sherrill, J. G. & Hall, D. P., 1940. *Am. J. Surg.*, 48, 669.
 Siris, I. E., 1941. *New York State J. Med.*, 41, 571.
 Smithly, H. G. & Charlston, S. C., 1943. *Surg.*, 13, 122.
 Slany, A., 1940. *Deutsche Ztschr. f. Chir.*, 253, 495.
 Sprout, J., 1936. *Am. J. Roentgenol.*, 36, 910.
 Wirtz, C. W. & Lyon, B. B. V., 1941. *Amer. J. Digest. Dis.*, 8, 246.

Gastric Acidity In Apparently Healthy Individuals

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FOR the past fifteen years, fractional gastric analyses have been run as a part of the fundamental course in physiological chemistry at this university. Normal healthy students have served as subjects, and gastric contents have been collected according to standard procedures after feeding of either the Ewald or the alcohol test meals.

Data obtained by determining the gastric acidity of such samples bear little similarity to the so-called normal values of modern textbooks. Likewise, there does not appear to be too much similarity between the normal values as given in the various standard textbooks of clinical pathology or of physiological chemistry. The curve for normal gastric acidity is usually described as

TABLE I
Normal Values for Gastric Acidity as Listed in Various Standard Texts

Author	Maximum Total Acidity		Maximum Free Hydrochloric Acid	
	Degrees	Min. after Meal	Degrees	Min. after Meal
Best & Taylor ¹	35-70	60 or 60 through 90	20-40	60 or 60 through 90
Gradwohl ²	40-60 or 70	60-90	20-40	60-90
Harrow ³	75-100	50% of total acidity
Kolmer & Boerner ⁴	40-60	60-90
Mathews ⁵	74-90 or 100	*	40-70	*
Stitt, Clough & Clough ⁷	50-80 or 100	25-50
Todd & Sanford ⁸	50-100	25-50
Mattice ⁶	60-80	30-40

Hawk & Bergheim⁹ present typical curves but list no values.

*Values determined for a single sample withdrawn 45 minutes after the test meal.

a parabola reaching its maximum value from 60 to 90 minutes after the time of ingestion of the test meal, with the free hydrochloric acid following a similar pattern. A brief summary of the "normal" data in text books may be found in Table I.

For the purpose of comparison, gastric data obtained from fifty apparently healthy persons, used as subjects, have been compiled to form Table II. These data are arranged in order of ease of comparison of increasing maximum total acidity. The curves for total

acidity are listed as normal in shape if they resemble a parabola. It should be mentioned that the subjects were not permitted to swallow their saliva during the experiment.

Inspection of Table II reveals the following: Sixty per cent of the curves for total acidity (30) are of the shape described as normal. Of these thirty curves described as normal in shape, nineteen reached the maximum total acidity in less than 60 minutes. Since all of the standard textbooks listed in Table I state that the normal individual does not reach a maximum value for total acidity until at least 60 minutes after eating the test meal, when both the shape of the curve and the time of occurrence of maximum total acidity are considered, the number of normal cases in the present study is reduced to 11 (22 per cent). However, a maximum total acidity of 35 degrees or more (lower range in value listed by Best and Taylor¹ and the lowest value given in any standard textbook in Table I) was present in only 8 of the 11 cases. Thus, the gastric data for total acidity in only 16 per cent of our apparently healthy subjects correspond to the normal values given in standard textbooks.

The values for maximum acidity in 38 of our subjects (76 per cent) were between 20 and 60 degrees, considerably lower values than those listed in the majority of standard textbooks. Maximum value for any subject was 90 degrees. More than half of the total number of subjects (52 per cent) reached their maximum total acidity by the end of 45 minutes, instead of after 60 minutes. The maximum values for free hydrochloric acid in our subjects agree with the textbook values somewhat better than the values for total acidity. In 29 subjects (58 per cent), the maximum free hydrochloric acid was between 29 and 50 degrees. However, 28 (56 per cent) of the total number of subjects reached their maximum value in less than the 60-minute interval said to be normal.

Because these results varied so greatly when compared with each other and with published standards, an investigation was recently conducted in which a few individuals were used repeatedly as subjects for fractional gastric analyses. These persons were in good health and had had no digestive disturbances. They reported from time to time for gastric analyses which were made after a test meal of crackers and water. The results of repeated gastric analyses on the same subject are presented in Table III.

These data show that the same values are not obtained when analyses are repeated on different days with the same subject. With subject H. U. four out of

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TABLE II
Gastric Acidity Determinations for 50 Apparently Normal Students

Sub- ject No.	Sex	Type of Test	Shape of Curve of Total Acidity	Maximum Total Acidity		Maximum Free Hydrochloric Acid	
				Meal	Degrees	Min. after meal	Min. after meal
1.	M	Ewald	#1	19.2	75	11.0	75
2.	M	Ewald	N	20.0	60	15.0	60
3.	M	alcohol	N	21.0	30	12.0	30
4.	M	Ewald	N	22.0	30	19.0	30
5.	M	Ewald	#3	24.5	45	14.0	30-45*
6.	F	alcohol	#3	26.0	45	18.0	45
7.	M	Ewald	N	27.0	15	19.0	15
8.	M	Ewald	N	27.0	60	15.5	60
9.	M	alcohol	N	29.0	60	19.0	60
10.	F	Ewald	#3	29.2	90*	27.0	90
11.	M	alcohol	N	30.0	30-60*	18.0	45
12.	F	alcohol	N	31.0	30	28.0	30
13.	M	alcohol	N	31.0	45-60*	26.5	45
14.	M	Ewald	N	32.0	30	27.0	30
15.	M	Ewald	N	32.0	45	23.0	45
16.	M	Ewald	N	34.0	15	24.0	15
17.	M	Ewald	#1	35.0	45	25.0	45
18.	M	Ewald	#1	36.0	15	27.0	15
19.	M	alcohol	#3	36.5	60	25.0	60
20.	M	alcohol	N	37.5	30	30.0	30
21.	M	Ewald	#1	37.5	60	31.0	60
22.	M	alcohol	N	38.0	60	32.0	60
23.	F	alcohol	#1	38.1	90	27.0	90
24.	F	alcohol	ladder-shaped	39.0	90	19.0	90
25.	M	Ewald	N	40.0	30	32.0	30
26.	M	alcohol	#3	40.0	45	27.4	45
27.	M	alcohol	#3	40.0	60	40.0	60
28.	M	alcohol	N	40.0	75	30.0	30-75*
29.	M	Ewald	#4	42.0	90	31.0	90
30.	M	alcohol	#1	44.0	90	18.0	45
31.	F	Ewald	#1	44.0	90	34.0	90
32.	M	Ewald	N	45.0	30	31.2	30
33.	M	Ewald	#3	46.0	75	28.0	45
34.	M	Ewald	#1	47.0	30	41.0	30
35.	M	alcohol	N	48.0	60	40.0	60
36.	M	alcohol	N	51.0	30	44.0	30
37.	M	Ewald	#4	56.0	15	48.5	30
38.	M	alcohol	N	57.0	75	42.0	75
39.	M	alcohol	N	60.0	60	44.0	60
40.	M	Ewald	N	62.0	60	30.0	60
41.	M	alcohol	N	63.0	45	53.0	45
42.	M	alcohol	N	67.0	45	60.0	45
43.	M	alcohol	N	72.0	45	65.0	34
44.	M	alcohol	N	74.6	60	70.0	60
45.	M	alcohol	N	75.0	30	68.5	30
46.	M	alcohol	#2	75.0	90	50.0	90
47.	M	alcohol	N	82.0	60	72.0	60
48.	M	Ewald	#1	82.0	90	42.0	90
49.	M	alcohol	N	89.0	30	83.0	30
50.	M	Ewald	N	90.0	45	83.0	45

*The maximum acidity was maintained during the time indicated.

Lactic acid was absent in all cases.

N=Normal-shaped curve.

#1=first part of curve is a parabola, but curve rises again at end of experiment.

#2=center of curve depressed giving rise to two parabolas.

#3=rising curve.

#4=inverted parabola.

five curves for total acidity were of a type described as normal. This was the greatest number of similar curves for any subject in the experiment. Subjects P. A., C.

K., B. M., and W. R. each had only two so-called normal curves for total acidity.

Individual variation in maximum total acidity was least in subject M. W. (12.8°), who participated in only three analyses. Subject H. U. on six occasions showed less variation (13.4°) than the remaining subjects, while variation was greatest in the case of B. M. (45.86°). The average variation in the 13 subjects was 28.19°. Maximum total acidity in all subjects varied from a high value of 101.86° for subject B. M. to a low of 24° for subject D. M. Average value for the 72 analyses on all subjects was 69.75° and in 63 cases (88-

TABLE III
Repeated Gastric Acidity Determinations for Thirteen Subjects

Subject	Date of Sex Analysis	Shape of curve for total acidity	Maximum Total Acidity		Maximum Free Acidity	
			Degrees	Min. after meal	Degrees	Min. after meal
PA F	1-21-43	N	64.0	60	33.6	90
	1-29-43	*1	59.8	30	34.8	45
	2- 1-43	*1	59.0	90	33.6	60
	2- 3-43	N	62.8	75	33.2	60
	2- 8-43	*2	45.0	75	32.6	90
	2- 6-43	*1	67.2	90	41.0	90
MB F	AVERAGE		60.1	70	34.8	72.5
	MAX. RANGE		19.2		8.4	
DG F	1-27-43	N	26.0	60	36.0	60
	2- 1-43	*3	83.2	90	49.8	90
	2- 3-43	N	90.0	60-75	30.0	75
	2- 8-43	*1	81.0	60	36.0	60
	2-17-43	*1	78.2	90	38.0	90
	AVERAGE		86.5	69.1	45.2	75
CK M	MAX. RANGE		17.3		25.0	
BM M	1-22-43	N	41.4	60	32.2	75
	1-27-43	*1	87.4	75	31.4	75
	1-28-43	*2	72.0	60	36.0	75
	2- 1-43	*1	62.0	10	39.0	75
	2- 2-43	*1	55.0	90	39.0	60
	2-19-43	N	41.4	45	33.4	30
DN M	AVERAGE		66.9	60	35.1	60
	MAX. RANGE		39.4		35.0	
CK M	ladder-shaped					
	1-18-43		94.0	75	54.2	75
	1-23-43	*2	82.6	45	72.0	75
	2- 4-43	N	86.0	45	45.2	60
	2- 6-43	N	74.0	10	27.0	45
	2-10-43	*1	36.00	90	51.00	90
BM M	2-12-43	*1	98.00	60	74.00	60
	AVERAGE		82.6	52.5	44.5	67.5
	MAX. RANGE		31.0		25.0	
DN M	1-21-43	N	55.0	75	26.8	90
	2- 3-43	N	96.67	75	72.02	75
	2- 5-43	*2	94.20	75	90.00	75
	2-10-43	*1	36.00	90	51.00	90
	2-12-43	*1	98.00	60	74.00	60
	AVERAGE		85.3	70	69.83	70
JM M	MAX. RANGE		43.86		39.0	
WM M	1-21-43	N	53.8	45	36.0	45
	2-13-43	N	74.0	60	42.0	75
	2-17-43	*3	61.6	90	27.2	90
	2-19-43	N	80.0	75	32.0	90
	2-24-43	*4	70.8	90	43.0	90
	3- 3-43	*3	63.2	75	38.2	45
JM M	AVERAGE		67.2	73	39.7	73
	MAX. RANGE		26.2		24.8	
WM F	4- 6-43	N	71.0	45	55.2	75
	4- 8-43	*2	68.2	60	46.8	60
	5- 8-43	N	72.2	45	58.8	60
	5-18-43	*1	80.2	60	60.8	60
	5-31-43	N	45.0	60	14.6	60
	AVERAGE		67.3	54	51.2	63
WR F	MAX. RANGE		35.2		26.2	

Subject Date of Sex Analysis	Shape of curve for total acidity	Maximum Total Acidity		Maximum Free Acidity	
		Degrees	Min. after meal	Degrees	Min. after meal
DS F 1-27-43	ladder-shape	48.0	45	27.0	90
1-30-43	*1	81.8	45	42.0	45
2-3-43	N	66.6	75	37.0	75
2-5-43	N	67.0	60	37.0	75
2-10-43	N	71.0	60	41.0	75
2-12-43	N	54.8	45	23.4	45
AVERAGE		64.9	55	34.6	67.5
MAX. RANGE		43.8		18.6	
GS M 1-28-43	*1	93.2	45	67.2	90
1-29-43	N	90.8	75	76.4	90
2-3-43	N	75.0	45	47.0	60
2-4-43	*1	97.2	60	85.0	90
2-8-43	*2	88.0	75	57.0	90
2-11-43	N	71.0	45	46.0	90
AVERAGE		85.8	55	63.1	85
MAX. RANGE		26.0		39.0	
HU M 4-12-43	N	54.6	60	36.8	60
4-29-43	*1	53.4	60	24.0	90
5-18-43	N	59.0	45	29.97	75
5-20-43	N	61.6	45	24.0	90
6-3-43	N	66.8	45	39.4	60
AVERAGE		59.1	51	30.8	75
MAX. RANGE		13.4		15.4	
MW F 4-17-43	N	65.4	60	36.6	60
4-19-43	N	78.0	45	50.0	45
4-26-43	*2	75.2	75	47.0	75
AVERAGE		73.7	60	44.5	60
MAX. RANGE		12.8		13.4	

*1—First part of curve, a parabola but curve rises again at end of experiment.

*2—Center of curve depressed giving rise to two parabolas.

*3—Rising curve.

N—Normal-shaped curve.

89 per cent) the maximum total acidity fell between 50° and 99°.

Most of the subjects did not show as great an individual variation in free hydrochloric acid as in total acidity. P. A. (8.4°) and again M. W. (13.4°), and H. U. (15.4°) were the subjects with the least individual variation, while subject C. K. (45°) showed

the greatest variation. The average variation in the 13 subjects was 24.2°. Maximum free hydrochloric acid for all subjects varied from a high value of 90° (subject B. M., also highest in total acidity) to a low value of 13.4 (subject P. A.). Average value for the 72 analyses was 43.1° and in 61 of them (85 per cent) the maximum total hydrochloric acid ranged from 20° to 60°, twenty-five per cent were between 30° and 40°.

These subjects required a somewhat longer time to reach their maximum acidities than the original group of 50. In this respect, the analyses agree more closely with the textbook values.

SUMMARY

1. Gastric data, including maximum total acidity, maximum free hydrochloric acid, the time of occurrence of each, and the shape of curve of total acidity have been presented for 50 apparently healthy subjects.

2. Similar gastric data obtained by repeated analyses on 13 apparently healthy subjects are also included.

3. Comparisons have been drawn between the so-called normal values listed in modern textbooks and those actually obtained from the two groups of apparently healthy subjects.

CONCLUSIONS

1. The variations in normal gastric acidity are far greater than the variations listed in standard textbooks.

2. There is considerable variation in the gastric acidity in the individual subjects as shown by repeated analyses with the same subject, carried out at intervals of a few days.

REFERENCES

1. Best & Taylor, *Physiological Basis of Medical Practice*, 3rd Ed., Williams & Wilkins, Baltimore, 1943, p. 736.
2. Gradwohl, *Clinical Laboratory Methods and Diagnosis*, 2nd Ed., The C. V. Mosby Co., St. Louis, 1938, pp. 578-582.
3. Harrow, *Laboratory Manual of Biochemistry*, W. B. Saunders Co., Philadelphia, 1940, pp. 42-43.
4. Kolmer & Boerner, *Approved Laboratory Technic*, 3rd Ed., Appleton Century Co., New York, 1941, p. 205.
5. Mathews, *Physiological Chemistry*, 6th Ed., Williams & Wilkins, Baltimore, 1939, pp. 598-599.
6. Mattice, *Chemical Procedures for Clinical Laboratories*, Lea & Febiger, Philadelphia, 1936, pp. 324-326.
7. Stitt, Clough and Clough, *Practical Bacteriology, Haematology, Parasitology*, 9th Ed., P. Blakiston's Son & Co., Inc., Philadelphia, 1938, pp. 754-5.
8. Todd & Sanford, *Clinical Diagnosis by Laboratory Methods*, 8th Ed., W. B. Saunders, Philadelphia, 1943, p. 455.
9. Hawk & Bergelin, *Practical Physiological Chemistry*, 11th Ed., P. Blakiston's Son, Philadelphia, 1937, p. 304.

Malnutrition -- Causing General Lowered Tissue Resistance and Local Tissue Pathology

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THIS paper is submitted without details or reference, to research men and clinicians for consideration and criticism of the theory advanced.

The presented theory is that dietary deficiencies, especially of essential nutrients over a prolonged period of time, may cause a general lowered resistance of body tissues. This lowered resistance to trauma and disease may be the primary cause of a number of widespread

disabling illnesses in which the etiology is now obscure, such as allergy, peptic ulcer, nephrosis, malignancy, etc. Further, it may be the principal underlying cause determining the severity of symptoms and signs in some illnesses known to be due to bacterial or virus infection, as rheumatic fever, nephritis, poliomyelitis, etc.

The cause of the abnormal tissue status hinges on liver dysfunction. Recent research indicates that the highly specialized cells of the liver parenchyma are

readily damaged by dietary deficiencies. Increasing degree of deterioration of these cells is associated with an increasing degree of lowered metabolic organ function and sluggish excretion, and so there is incomplete preparation here of even available nutrients, partially due to interlocking action, for the further metabolic changes which occur in the tissues. This leads to abnormal tissue metabolism. An early related effect is development of poor intestinal absorption, which further tends to lessen the body food supply. No doubt resulting glandular imbalances, with abnormalities in secretion, are an important factor in causing specific lowered tissue resistance.

In this abnormal state the various tissues are readily damaged by minor injuries and easily sensitized to specific or non-specific irritants with which the tissues may come in contact continually or repeatedly. A chronic or chronically recurring lesion or local tissue pathology develops, as occurs for example, in cases of peptic ulcer.

Though a body food surfeit tends to cause sluggishness and stasis, with resulting general lowered efficiency of body functions, especially in the elderly subject, it would seem that in these, and more particularly in the young growing individual, deficiencies are more pernicious in their incidence. And even obesity, if it is ever explained, may be found to be more frequently due to deficiencies in the diet causing abnormalities in assimilation than to excess food consumption. Again, given a well-balanced diet, excess food intake is less likely to occur. Capricious appetite is often a result of habitual serving of poorly balanced meals. Improvement in these may effect disappearance of anorexia, or on the other hand result in toning down an appetite which is "too good".

As to why one classification of tissue is chiefly affected, or a particular type of pathology develops in any disease entity due to malnutrition, is not clear. For example, though rheumatoid arthritis is considered to be a disease affecting many parts of the body, the principal disability and classical lesion occurs in the joints. In neuritis in malnutrition the nerves may be the only or chief complaining tissue. Again local affections occurring in the gastric mucosa may remain benign for years; in other cases early malignancy develops. Possibly specific nutrient deficiencies may be found to account for tissue selection and for the nature of the resulting pathology.

"Food, the magic cure-all" is a frequently heard explanatory remark. "Many a truth has been spoken in jest", and advancing scientific knowledge may prove that when external influences harmful to the human organisms are omitted, food may be very nearly this. Eliminating major injuries, infections, chemical poisoning, tropical diseases, etc., it may later be proven that, climate being constant, a good food and water intake, with oxygen sufficient for the internal combustion involved, is the principal factor in successful treatment, curative and prophylactic, of most other current human ailments and disabilities. Its importance is immense in development of immunity and positive general body defense and resistance against disease and trauma.

To begin with, obscurity of the etiology of foetal malformations, congenital glandular imbalances, and hereditary psychotic tendencies, when these are not caused, at least theoretically by infection, justifies search for dietary deficiencies as the cause. In the individual investigation, examination of the family tree, if traceable, may reveal a long line of underfed or badly fed ancestors. In these, history of certain continuing symptoms and signs may point to poor nutrition as the causal genetic factor in the psychoses, allergy, cancer and other diseases in which there are considered to be family tendencies or predisposition.

Conversely, it would appear that families who have lived non-intermittently through generations, including the present one, on the "fat of the land", or rather on the fat plus all else that goes to form a balanced diet, are healthy. Here may be found whole families of physically and mentally healthy and emotionally balanced people of poised personality—and possibly superior intellect—at least on an average.

Food is of prime importance in our scheme as the source of building and repair material, body heat and energy, and as the form in which the elements are supplied by means of which the body recreates itself. In case of trauma, medical science cannot even direct damaged tissue repair, but can at best supply favorable local and general environment as an aid to natural forces at work in this regard. In such environment, for best results good food is of paramount importance. Exact functions or body requirements of many nutrients, even under normal conditions, have not as yet been determined. So in regard to nutrition, medicine is still to a considerable extent working in the dark, though science, through fact-finding experiment, is at an ever-increasing rate, shedding light of newly acquired knowledge on the subject.

At present we do not know how to intelligently appraise findings in nutritional surveys. It is suggested that in the meantime the nutritional goal should be that every individual citizen be provided a generous balanced diet.

On the one hand then good food must be regarded as essential for sound foundation and strong structure in body building, repair, and upkeep; on the other hand there is at present a state of incomplete scientific knowledge regarding nutrient requirements in normal body metabolism. Also, there is at present incomplete knowledge regarding numberless body nutrient chemical reactions, interactions and functions. In view of this, it is logical to consider the possibility of, or even to expect a high incidence of all possible grades of body weaknesses, disorders and dysfunctions associated with all grades and degrees of symptoms and signs of illness, from the mild subclinical to alarming or fatal, when the food intake is low or lacking in, or there is poor absorption or abnormal assimilation of, any nutrient which is essential to life or to optimal health. This is applicable whether the missing nutrient is essential as a body building material, as a source of heat and energy, or may act only as a catalyst or enzyme.

With this presented idea in view, a number of illnesses are briefly discussed:

The etiology of chronic gastric ulcers and gastric carcinoma are still obscure. It is recognized that both affections are most commonly situated primarily along the lesser curvature in the pyloric region of the stomach. This location is in the gastric pathway which runs from the cardiac to the pyloric opening, and is demarcated from the rest of the stomach by oblique fibres of the muscular coat. "The mucosa of the gastric pathway is more firmly attached and more tightly stretched than elsewhere in the stomach. Experimental lesions in this region heal more slowly than in other parts." It is possible that mechanical food irritation, or more reasonably that prolonged angio-spasm brought on in this "mirror of emotions" by emotional tension, which is commonly a frequently recurring symptom in these cases, causes the initial mild injury. Complete healing of the lesion is prevented primarily by lowered tissue resistance due to malnutrition, and secondarily by the mechanical pressure of the stretched mucosa and by the local lowered blood supply, caused again by the stretched mucosa. This condition is enhanced during emotional spasm, and a vicious circle develops. Local discomfort and pain causes general nervous excitability, which in turn causes increased gastric secretion, especially of the H Cl., and increased gastric mobility and muscular spasm, all of which tend to aggravate and increase the initial local pathological condition. Normally these lesions, if occurring at all, would heal quickly; in case of malnutrition they frequently develop into chronic lesions associated with an increased degree of tissue destruction.

The rationale of this supposition has support, in that at least some cases of peptic ulcer clear up completely—accompanying nervous symptoms and all—when the patient is prescribed a generous full balanced diet. This diet includes normally sufficient bulk, proteins, fats, carbohydrates, vitamins, minerals, calories and fluids. Recovery to normal is speeded by addition to the diet of pharmaceutical preparations containing more or less massive doses of vitamins A, D, C and the B complex and an iron salt. Liver extract for oral administration is prescribed routinely here, and in some cases for intra-muscular administration as well. In cases where there is marked indication for chologogue therapy, best results from dietary treatment are only obtained when the chologogue is also prescribed. Best therapeutic results from chologogue therapy would seem to be obtained when doses large enough to cause relief of upper abdominal discomfort within an hour or so are used. Here it is given one hour before a meal with a drink of warm water. It is prescribed once daily for four days, then two or three times weekly for three weeks, then once weekly indefinitely if indicated. In some cases large doses are given daily for a few days periodically.

The question arises: can gastric ulcers and gastric carcinoma be prevented from developing simply by prevention of specific and non-specific general malnutrition in body tissues? If so, it is suggested that liver dysfunction is a primary effect of dietary deficiencies. From this, as well as from the deficiencies, results the abnormal glandular functions and general lowered tissue resistance.

In cancer of the body surface tissues, it is recognized that initial trauma and chronic local irritation frequently precede development of the primary tissue malignancy. This is typically true of cancer of the lower lip in men. Its development has usually been preceded for years by local irritation, caused possibly by an old pipe or a jagged tooth.

It is stated authoritatively too that carcinoma of the cervix uteri is preceded, usually if not always, by chronic tissue irritation and local infection which has developed following improperly repaired cervical lacerations during childbirth.

It is also recognized that breast carcinoma often does not present this history of previous tissue injury and pathology, "but breast carcinoma occurs chiefly during the involution period just preceding the menopause when the breast normally undergoes atrophic changes with disappearance of the glandular tissue." Other cases occur during and after the menopause. "It is considered that the exciting cause which starts malignant neoplasia here, at this time of marked breast changes, is connected with ovarian stimulation, since removal of the ovaries in young mice of a race with high incidence of breast carcinoma will prevent the development of the carcinoma." This stimulation may be considered as a cause comparable to the trauma irritation which precedes development of, for example, lower lip carcinoma and carcinoma of the cervix uteri.

Since malignancy does not develop in all cases subject to local chronic irritation, it is again suggested that the underlying cause in cases where it does develop may be glandular imbalances and general lowered tissue resistance due to malnutrition of some order. Further, the theory may apply in instances of occurrence of carcinoma and sarcoma in internal organs. In bone a mild trauma, or even a slight capsule pressure or irritation to which the tissues is exposed repeatedly, as from pull of attached muscles occurring during normal muscular movements, may start the initial irritation which results in neoplastic changes in an already abnormal tissue. So in other malignant affections the idea is advanced that they would not occur, or in any case be far less common, in really well-nourished individuals. Certainly malignancy occurs in some patients who have a cancer-free family history. One such case of advanced carcinoma was recently seen in this practice. In this instance there was no known history of cancer in the ancestry. This patient's diet was found, for various reasons, to have been very low in a number of nutrients over a period of years preceding and during the development of a double breast carcinoma.

In allergy there appear to be areas of local lowered resistance, or areas of tissue sensitized to one or a number of allergens. The frequency of occurrence of associated symptoms of malnutrition other than the local sensitivity and pathology, as well as the favorable response to dietary treatment in at least some cases, supports the supposition that the etiology of the condition is some order of malnutrition.

A few chronic cases, treated along the lines suggested, have proved refractory to treatment, though the patients' general health was benefitted. In such cases

where treatment was fully carried out, it is considered that possibly during the long course of the chronic affection, irremediable organic tissue pathology had developed in the affected tissue, or possibly in the cells of the liver parenchyma or in some gland or glands of internal secretion.

Three cases of allergy successfully so treated are briefly reviewed:

Case 1—Hay Fever

L. K., female patient, age 11 years when first seen, February 1943. E. C.—fairly marked abdominal discomfort and fatigue. Both symptoms had been present frequently for two or three years. There was no head cold at this time. History: Patient had had severe hayfever—as diagnosed by her physician—during a considerable part of summer of 1941 and the summer of 1942.

P. X. was chiefly negative, except for considerable tenderness on palpation in the right upper quadrant of the abdomen.

Treatment: Effective cholagogue therapy. Generous balanced diet, to include three large oranges daily. Pharmaceutical preparations of vitamins A, D and the B complex and an iron salt.

March, 1944: Mrs. K. reported that the patient had been very well since the visit to the clinic in February 1943. All treatment had been carried out as directed. There was no hay fever during summer of 1943. There has been no unnatural fatigue nor abdominal discomfort since a day or two after the clinic visit in February 1943.

Case 2—Asthma

Pt. B. B., male patient age 9 years at first office visit, November 12, 1941.

Asthma had been diagnosed by an allergy and child specialist at one year of age. The severity of the attacks of dyspnoea had increased at age of four years and were most troublesome during winter. During the summer and fall of 1941 the asthmatic attacks became very severe and occurred every ten to fourteen days. Between attacks there was mild dyspnoea frequently. Skin tests had indicated sensitivity to a number of substances, but most marked to ragweed. The boy was tired all the time and did not run or join in sports. Eggs had been eliminated from the diet. The appetite was poor and the diet was very suggestive of deficiencies. Some days he had one or two small oranges; often none. Except Ephedrine, no pharmaceutical preparation had been prescribed. The mother thought that vitamins were less expensive at the grocery than at the drug-store.

The boy was first seen several days after a severe attack of asthma, and the parents thought he was about to have another.

P. X. There was a moderate degree of dyspnoea. The boy was pale and underweight. Many wheezes were heard all over the chest on auscultation. He volunteered that upper abdominal pain was distressing during attacks. At this examination there was slight but definite tenderness on palpation in the right upper quadrant of the abdomen. Treatment: Cholagogue therapy; body skin exposure to ultra violet rays—es-

pecially the chest wall—one treatment. Pharmaceutical preparations containing vitamins A, D and the B complex, an iron salt, and three large oranges daily. A generous balanced diet. Full participation in outdoor sports at school after two weeks' treatment. Neither Ephedrine nor Adrenaline were prescribed.

Feb. 4, 1942: The patient improved rapidly following the first office visit. There has been no dyspnoea since, nor upper abdominal discomfort. The appetite is good. There has been some weight gain. The boy feels and looks well. He is very active, and joins in sports at school.

February 1943: The patient is well. After the first three months of treatment the novelty wore off and treatment was neglected. During spring and summer of 1942 there were occasional mild attacks of dyspnoea. The patient was seen in a number of these and it was found that the diet was again low in vitamin C and other nutrients. Improved diet again resulted in relief of the dyspnoea.

Case 3—Asthma

A. M., female patient, age 12 years at the time of first consultation, October 2, 1943.

For two years this girl had been subject to asthmatic attacks, as diagnosed by her physician. There was prolonged dyspnoea, especially toward the end of the week after a week of school activity. The attacks were most troublesome in winter. Colds and coughs were very frequent. Fatigue was very troublesome at school, and she frequently had a sensation of fullness and pain in the upper abdomen. Ephedrine tablets had been prescribed for the asthma P. R. N. by her physician.

P. X. This was a bright girl who frequently topped her class in school grading. There was mild dyspnoea at this examination, and wheezes were heard all over the chest on auscultation. Relief was afforded by Adrenaline administration. Slight tenderness was elicited on abdominal palpation in the right upper quadrant. The examination was otherwise essentially negative.

Treatment prescribed included cholagogue therapy in effective dosages, pharmaceutical preparations containing liver extract, and vitamins A, D and the B complex and an iron salt. A generous balanced diet was outlined, to include three large oranges daily.

Progress: December 29, 1943. First return clinic visit. The patient is very well. The appetite is good. There have been no colds or coughs for weeks. On examination, the chest is clear today. On November 20 she wakened in the early morning with a moderate degree of dyspnoea, which lasted four hours, and was relieved by Ephedrine. This attack was milder than the attacks she had been having every week or so for two years. It was the only one she had between the first clinic visit on October 2nd and this one on December 29th.

March 1, 1944: M. came to clinic because she had had mild dyspnoea all night. This is the first attack since November 20, 1943, as described above. All medications had been discontinued for past few weeks—all during February.

May, 1944: Improved diet was again followed by relief of the attacks of dyspnoea.

As mentioned, a number of cases of eczema and migraine have been successfully so treated. A smaller number have been found refractory to this treatment. A case of Cholecystitis is cited here:

Mrs. H. A., age 28 years at first office visit, December 1, 1939. Four years previously her physician had diagnosed cholecystitis—without stones. A cholagogue and low carbohydrate diet had been prescribed. There were during these years almost daily attacks of upper abdominal discomfort with a sensation of distention and, less frequently, attacks of subacute pain. The cholagogue therapy had done little to relieve these.

P. X. was chiefly negative. The patient had been previously active in sports. She was a bright young woman, but appeared very unhappy and felt sluggish. The complexion was sallow, B. P. low. Patient was underweight. Headaches were frequently troublesome. Blood and urine examinations were negative.

Treatment included effective cholagogue therapy. A moderately high carbohydrate, low fat and no meat diet was prescribed for a few weeks, then a balanced generous full diet. An iron salt and the usual vitamin preparations, with daily outdoor exercise, were prescribed.

February 16, 1940—second office visit: The patient had found considerable early relief with the cholagogue therapy prescribed, so increased dosage on her own initiative on the theory that if small doses were good, large ones were better, and she was determined to regain buoyant health. In any case, two ounces of the concentrated solution of sodium phosphate were taken in single daily doses for several days; then smaller doses were taken less frequently.

There has been no abdominal discomfort for six weeks, nor headache. There has been a weight gain of eleven pounds.

March, 1944: The patient is very well. The only attack of upper abdominal discomfort there has been since February 1940 was toward the end of a pregnancy in 1941, when cholagogue therapy quickly relieved it.

A number of cases so diagnosed as cholecystitis have been thus treated and permanently relieved by effective cholagogue and dietary treatment. This is true in a number of cases where cholecystectomy had been performed without relief of symptoms.

Observations on a case of Nephrosis:

B. M.—female patient, age 23 months when first seen, January 1942. This child had just spent two months in a large clinic hospital and was discharged against advice, as the parents wished to have the child home. Prognosis was guarded. No improvement had been noted in the patient's condition during stay in hospital.

The case was typical of nephrosis occurring in childhood. The temperature was normal as a rule. There was widespread fluctuating edema and ascites. Urinalysis—albumin 3-4 plus, hyaline and granular casts—occasional to few, and later many. Red blood cells and pus cells 1 to 2 to few. Blood-cholesterol 926 to

1042 mg. per cent. Blood urea varied from 22 to 74 mg. per cent. Blood protein 4.1 to 5.1 grams per cent., with albumin-globulin ratio ranging from 1:2.5 to 3:2.6.

Many medications had been given a trial in hospital. Patient was discharged on a high protein diet. No medications.

January 18–February 3: The child was in this city en route home and the parents were anxious to try any suggested treatment.

Treatment included effective cholagogue therapy and the usual vitamin and iron preparations.

Results—The urinalysis-albumin remained 4 plus. The child was much happier and peppier the first few days of treatment and the color improved. The swelling and itching of the eyelids was relieved by the cholagogue, also the head cold cleared. The edema was down and the weight. There was the usual increased urinary output associated with this lessened edema.

January 21, fourth day of treatment, the child seemed so well that, without advice, the mother took her out of doors in a baby carriage for one hour. This was followed by a severe recurrence of the head cold and of the edema.

January 22: temperature 103-140-28. For two or three days there was fever.

February 2: The daily urinalysis while in this city showed alb. + + + +. The child has been very happy the past few days again, but has developed an enormous appetite and is getting a high protein diet with large helpings of meat. The mother would not agree to giving a high carbohydrate, no meat, low fat diet. The first few days on the vitamin therapy she had refused meat, and at that time the edema and ascites were down. Today they are increased, and this is confirmed by a weight increase.

The patient left for her home in another Province February 3rd. Several months later there had been no improvement.

Remarks:

As to the efficacy of any treatment in Nephrosis, there are at least two schools of thought. Some men have found high protein diet beneficial; others have found "no special treatment" excellent therapy with complete recovery in a fairly large percentage of cases treated. Other men, as reliable, state that it matters little what treatment is prescribed, even high vitamin therapy is allowable, for all cases prove fatal in five to ten years, and others state that the affection is one stage of nephritis and that longevity is usually not more than two years from the onset of symptoms.

Nothing is learned from the above case, but a suggestion is offered here that malnutrition be considered and investigated as the primary cause of nephrosis. It is suggested that dietary deficiencies cause first a dysfunction of the liver cells, which in turn causes an abnormal metabolism in the tissues generally and a lowered resistance. In this instance the kidney tissue is thus chiefly affected.

The history of the above case is suggestive. This child was apparently fairly normal till age of 1 year, 3 months, though she was a mouth breather earlier. At this age she was ill with influenza (as diagnosed by her

physician) for a few days. She was prescribed dageenan gr. 3 O. H. for 2 days. The illness quickly cleared up, but there was a skin rash for a time. Two months later, at age 1 year 5 months, hay fever was diagnosed by the physician, and advice was that an early T. & A. operation should be done. One further point of interest here was that some months previous to the development of influenza the child had been prescribed a no-milk diet, for no known reason. The mother adhered to directions for a two-month period, when on her own initiative she added some milk to the diet.

The theory is offered that a toxin from the enlarged tonsils and adenoids had caused an initial damage to the liver cells, dietary deficiencies during the no-milk period had aggravated the condition, and the dageenan had caused further deterioration in already damaged liver cells. This supposition has support according to the advanced theory in that a possibly allergic rash and hay fever developed soon after the dageenan had been given.

The case outlined above was probably fairly far advanced, with associated permanent damage in the kidney parenchyma, before the cholagogue and the reinforced dietary treatments were given the short trial. If there is a liver dysfunction basis in the etiology, the diet should have been a high carbohydrate, moderately low fat, no meat, but otherwise balanced diet for a time. In any case the child was happier than before taking the diet; also the head cold and itching of the eyelids were relieved by the sodium phosphate solution. The effect of the treatment on the edema, if any; cannot be appraised.

It is further suggested that in glomerulonephritis, malnutrition as an associated factor in the etiology should be considered. Although the disease is recognized as being due as a rule to streptococcal infection, it is also considered to be an extrarenal infection. No bacteria are found in the kidney tissues, and the blood and urine are sterile. The primary infection is commonly in the throat. It is suggested that this infection, possibly through action of toxins, first damages the cells of the liver parenchyma, causing dysfunction here, which leads to specific abnormal tissue metabolism in which the kidney-tissue is most affected, with the resulting further toxin formation and kidney-tissue inflammatory pathology and the alarming general symptoms.

Poliomylitis: According to a recent article on poliomylitis, by Toomey: "pain in the abdomen occurs. The latter is caused by buckling of a paralyzed segment of gut with proximal distension. It is relieved by enemas or insertion of a tube and by applying turpentine stapes to the abdomen."

It is here suggested that this pain and distension in some cases at least may be caused by liver affection. The fact that the virus of poliomylitis is commonly harbored in the gastro-intestinal tract, even in many symptomless individuals, during an epidemic, supports this theory. The liver is a very closely associated organ, both as a digestive functional centre and organically through the portal blood circulatory system. The question is asked—in addition to the infection and af-

fection of the central nervous system in Poliomylitis, could there be a virus infection of the liver which has not as yet been demonstrated at P.M. in fatal cases; or may the virus toxin cause liver dysfunction in this disease?

Two cases of Poliomylitis are briefly outlined:
Case 1

B. A., female patient age 7 years. This was a bright girl from a moderately poor home of Dutch-Canadian parentage. For over a year during 1940-41 she had attended the outdoor medical clinic at the Winnipeg Children's Hospital. The appetite had been poor, and every few months for the past few years there had been attacks for a few days of fever, nausea and vomiting, always associated with constipation and vague abdominal pain. Routinely, she had been prescribed at the clinic a generous balanced diet, with vitamin concentrates and an iron salt to be taken periodically, but no cholagogue therapy. A physician had not been called in during the bilious attacks. Early in the summer of 1941 the patient suffered from dermatitis venenata following poison ivy contact. The affection was treated without cholagogue therapy, though more recently this treatment is employed.

August 23, 1941: This girl was seen in her home at noon. Temp. 102-116-18. She had been very well recently, but had vomited once during the night and awakened in the morning feverish and nauseated. There had been emesis twice in the forenoon. Other symptoms were mild frontal headache and slight abdominal pain. The bowels had been constipated for a day or two. Once in the morning, on questioning, she said her neck was sore, but later denied it.

P. X., except for the fever, was chiefly negative. Throat—negative. The neck was not sore. The neck and back were normally flexible. There was no tenderness noted. The abdomen was negative on examination, though the patient insisted that there was vague pain and discomfort in the abdomen in no particular region. Incidentally, a few cases suffering from vague abdominal pains, but in which no tenderness could be elicited in the right upper quadrant on abdominal palpation, have benefitted from cholagogue therapy.

Treatment: Dagenan in moderate dosage was prescribed O.H. for several doses. The following day, August 24th, the temperature was normal. In two or three days the patient was quite well. This illness, the mother thought, was similar to, but a little more severe, than the bilious attacks to which the patient was subject periodically.

April, 1942: The girl was brought to the outdoor medical clinic. Shortly after the illness in August 1941 the mother noticed that she began to sit in a slumped position. This posture had become habitual and more pronounced, according to the mother, during the winter. A physician had not been consulted.

Examination revealed definite weakness of some of the back muscles. The case was referred to the orthopaedic clinic, where a diagnosis of poliomylitis as in August 1941, was made.

Kenny treatment was instituted; recovery of muscle tonus and function was complete in a few months.

May 25, 1944: The mother telephoned that the patient had developed an itchy rash following a "bilious attack". She still suffers from these attacks periodically, but less frequently and less severely than formerly. It is proposed to prescribe cholagogue therapy.

A number of cases are reported of similar development of muscle weakness, without history of poliomyelitis or of any noticed illness. In a number of such cases seen in this practice, tenderness has been elicited in the right upper quadrant on abdominal palpation. It is suggested that in these cases, and in cases of severe acute poliomyelitis, investigation of liver dysfunction as an associated causal factor to infection in the central nervous system as a cause of the severe symptoms, signs and disabilities, should be considered. The liver dysfunction may be primarily due to virus infection here or to toxic affection or dietary deficiencies, or all three.

Incidentally it has been noted in a number of cases with various diagnoses, but which are considered to have malnutrition as an associated causal factor, that where intensified dietary therapy is instituted, without cholagogue treatment, symptoms have been increased, as occurred for example in a number of cases of eczema. An illustration of this point is shown too in the following case, in that the patient had been prescribed intensified dietary treatment for months before the development of poliomyelitis.

Case 2—Poliomyelitis

Male patient, age 4 years. This child was in hospital from October 24, 1942 to January 31, 1943, under the care of the Poliomyelitis department. Kenny treatment was routinely given. On examination the specialist had found widespread muscular involvement. There was marked spasm of the neck and back muscles, with marked tenderness. Other muscles found to be involved were both biceps, brachii, pectoralis minor, quadriceps femoris, hamstrings, adductors longus and gastrocnemii, and the abdominal muscles. Fomentations were ordered for nearly the whole body, excepting the head.

There was a great deal of pain in this case the first few days in the hospital. Patient cried out frequently at night as if in severe pain. There was considerable restlessness and sweating. The spinal fluid was negative.

Progress: Though there was marked, widespread muscular involvement in this case, response to treatment was good.

Physician's note on chart, September 29, 1943: Patient is a strong, robust, healthy boy. There is no sign of paralysis of any muscle.

Note: Apparently many cases with negative spinal fluid findings and without Anterior Horn Atrophy are diagnosed as poliomyelitis, as this case was.

I first saw this child in his home in the spring of 1942. He had large, ugly tonsils, and for some time had had frequent head colds and coughs. Incidentally, this was a "better class of poor home". During the summer of 1942 he was prescribed a generous balanced diet, plus periodic administration of pharmaceutical preparations of vitamins and an iron salt. He had been referred to a throat specialist and was slated for a T. and A. operation in September, but it was not done

because of a head cold and cough. From then till admission on October 23rd with poliomyelitis, head cold and cough were fairly severe. I saw the patient the day before admission to hospital. The pain was not very severe as yet, but he insisted that there was considerable pain in the mid-region of the abdomen, just distal to the umbilicus.

The first night in hospital the night nurse reports that "patient holds his hands over his abdomen when he cries, as if the pain centered there." Later the location of the most severe pain, according to the nurse's notes, varied from time to time, sometimes occurring in the arms, wrists, ankles, etc.

On November 16th, about three weeks after admission to hospital and the beginning of the Kenny treatment, I examined the patient's abdomen. There was fairly marked tenderness in the right upper quadrant. This tenderness varied in degree at later examinations. On admission the liver had been palpable one inch below the rib margin. The poliomyelitis specialist was cooperative and agreed to have cholagogue therapy given a trial.

November 18th: There was marked tenderness in the whole right side of the abdomen. The right rectus muscle was spastic. This time the patient cried when the abdomen was palpated and indicated that the pain was severe. He had been moving about from side to side freely in bed for some days.

November 13th: Nurse's notes report "Patient is unable to sit up without support."

November 20th to December 9th: A moderate daily dosage of cholagogue was administered per ora. On November 20th for the first time the nurse's notes state "the patient is able to sit up a short time without support." I do not know whether this was before or after the first dosage of cholagogue. A single dose of cholagogue, if effective in causing a flow of bile from the liver, could cause relief of upper abdominal pain and result in encouraging the patient to sit up.

On November 24th when I went into the ward the patient was sitting up without support, eating a large dinner. All during the nineteen days of cholagogue therapy there was varying degree of spasticity of the right abdominal muscles, and sometimes in the left. Although the patient usually said there was local soreness here, he did not show any sign that there was tenderness on palpation of the abdomen after the cholagogue was started.

The question arises, is the abdominal pain in these cases the usual pain which occurs in affected muscles in poliomyelitis, or is it caused, at least partially, by liver affection? Also, would these cases benefit by cholagogue and intensive dietary therapy?

In rheumatoid arthritis it is considered that chronic arthritis is part of a systemic disease and present treatment aims to restore normal functioning of all physiological processes. Since neither injury nor infection are known to be the cause, and since gastro-intestinal disturbances and liver dysfunction are common findings, it is suggested that malnutrition as the etiology may profitably be investigated. The good results obtained in Ertron therapy support this theory.

The following case is suggestive:

In 1940 an adult female patient was prescribed a barbiturate for a few weeks for insomnia occurring during an illness. This patient had had frequent attacks of discomfort for years, with a sensation of distention and pain at times in the upper right quadrant of the abdomen. This had been relieved by the dietary and cholagogue treatment as outlined in this article. During the course of the barbiturate therapy moderately acute pain, especially on movement, occurred in all the finger joints of both hands without visible local signs of arthritis. At the same time the upper abdominal discomfort recurred. The barbiturate was discontinued and in a few weeks the pain in the affected joints subsided completely; also the upper abdominal discomfort. Cholagogue therapy was prescribed to be taken periodically. In this case the barbiturate was prescribed periodically, and discontinued three times with similar results—during therapy—painful finger joints and upper abdominal discomfort. Since the barbiturate prescription has been discontinued, many months ago, there has been no pain in the finger joints.

In this case it is suggested that the liver cells had probably been permanently mildly damaged by malnutrition, and the narcotic, when taken, increased the affection in these cells.

In rheumatic fever, where infection is considered to be the etiology, the idea is advanced that early liver affection from infection, toxin affection, dietary deficiencies, or all three, may be a principal factor, through causing lowered tissue resistance, in the etiology of the alarming symptoms and signs which occur in this widespread disabling illness.

Further, in osteo-arthritis due to trauma or to arteriosclerotic changes causing local ischaemia, malnutrition as it primarily affects the liver cells may very well be a causal aggravating factor.

In essential hypertension, arteriosclerosis and the major psychoses, too, it is suggested that investigation along nutritional lines may yield worthwhile results.

In children attending the outdoor clinic, as well as in patients in the higher income groups, symptoms of mild physical disorders and of minor social maladjustments, vanish in many of the cases treated along nutritional lines as outlined, when the directions are fully carried out.

Thus, when organic cause is ruled out and foci of infection and glandular defects, especially hypothyroidism, are eliminated, enuresis, habit spasms and outright chorea, nail-biting and restlessness respond frequently to this treatment approach, by disappearance of the symptoms. This is true too of many vague chest, abdominal and limb pains of apparently inorganic

origin, and of headaches and sore eyes when no organic cause is found on examination. It is suggested that the difference between growing pains and outright rheumatic fever pains may be chiefly a matter of degree of affection.

Many of these cases respond to intensified, balanced dietary therapy alone. In cases, which incidentally are often seen in children, where there are frequent attacks of discomfort or pain in the right upper quadrant of the abdomen, associated with unnatural fatigue, optimal results are only obtained from dietary treatment when effective cholagogue therapy is prescribed as well.

A few cases of catarrhal jaundice and jaundice in young infants have been treated along these lines.

Also when organic defects, foci of infection and glandular causes are eliminated in patients so treated, if directions are fully carried out, head colds show a lowered incidence in the poorest home.

In a few cases so treated, where it was thought organic cause of symptoms had been eliminated, but symptoms persisted following treatment, gastric analysis revealed achlorhydria. In a number of others, headache, fatigue, and a sensation of coldness in a warm temperature remained. In these cases, though there was little other evidence of hypothyroidism, dessicated thyroid gr. 1 daily was prescribed for a few weeks, if tolerated. In some of these the appetite improved rapidly and other symptoms disappeared. The balanced diet then, including iodized salt, apparently early results in improved function of the thyroid gland.

In advanced malnutrition, patients are not always cooperative in following directions for treatment. In these, often, qualities of character are altered. Thus, natural interest and curiosity are replaced by apathy, reasonableness and determination by stubbornness, and tolerance by intolerance.

SUMMARY

The theory is advanced that dietary deficiencies, primarily through causing liver dysfunction, may result in glandular imbalances, with abnormal quantitative and qualitative secretion, and in a general state of lowered resistance to trauma and disease in the tissues of the human body.

It is further suggested that this lowered tissue resistance may be the chief or an associated cause in a number of illnesses of obscure origin. Also it is suggested that this abnormal tissue status may be an associated factor determining the severity of symptoms, signs and disabilities in a number of diseases in which the etiology is known to be a bacterial or virus infection.

With this idea in view, a number of illnesses, such as malignancy, poliomyelitis, nephrosis, nephritis, allergy, etc., are chiefly discussed.

A New X-Ray Method of Studying the Anatomy and Motility of the Stomach and Duodenum: Its Diagnostic Value

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IN studying the anatomy and physiology of the stomach the radiologist has the great advantage of seeing all the variations and mutations in its shape and size. With the aid of the x-ray he sees this muscular organ while it is functioning. He sees the living anatomy and the living physiology and, by means of roentgenograms, he is able to register all the anatomo-physiological phases and changes of the stomach.

It is curious that for three centuries most of the characteristics of the anatomy and motility of the stomach have been known by anatomists and physiologists. Their knowledge originated in studies of animal or human stomachs observed soon after death, in studies of the stomachs of animals during the different phases of digestion, and in observations made on the intact stomach with the animal's abdomen open under a bath of salt solution or on the stomach removed from the animal and kept in a warm oxygenated Locke's solution.

Disagreement still exists between anatomists, physiologists, gastroscopists, and radiologists as to the anatomy and motility of the stomach. Its extraordinary variations in size and shape are responsible for this discord. According to Cruveilhier (1843),¹ "The



Figure 1. Constriction of the pars pylorica at the borderline of its two segments. Prepyloric sphincter according to anatomists and Groedel.

human stomach presents innumerable varieties, from the stage of extreme contraction in which stage it does not surpass the volume of the duodenum which follows the stomach to the stage of the enormous dilatation when it fills up almost the entire abdominal capacity." Froriep² characterizes these variations in form and size in one brief sentence: "Only the change is constant."

For the purpose of orientation radiologists and clin-

cians divide the stomach by imaginary lines into the pars cardiaca or fundus, the pars media or corpus, and the pars pylorica or antrum. A straight line drawn through the esophagus to the greater curvature divides the fundus from the body of the stomach. The body of



Figure 2. Constriction in between the body and pars pylorica at the incisura angularis. The musculus sphincter antri according to Schindler.

the stomach is divided from the pars pylorica by the incisura angularis on the lesser curvature and an imaginary line which runs from the incisura angularis to the greater curvature.

According to gastroscopists the incisura angularis is a definite anatomical structure. Its existence is due to the musculus sphincter antri (Schindler³). This interpretation of the incisura angularis is rejected by the great majority of roentgenologists.

The existence of the musculus sphincter antri (also called the pre-pyloric sphincter) has been known since 1679, when Wepfer⁴ described it for the first time. Later Spallanzani, Haller and others also observed it. Only concerning its location do opinions differ, a fact which I can readily understand after my own observations. In 1886 Hoffmeister and Schultz⁵ described the sphincter antri pylorici observed in isolated stomachs of animals, and Cathcart⁶ demonstrated its existence in dogs. Beaumont⁸, however, gave the first complete physiological description of his so-called transverse

band in man. Aschoff⁵, in 1918, published a study of the isthmus ventriculi observed in the human stomach soon after death. According to his observation, that

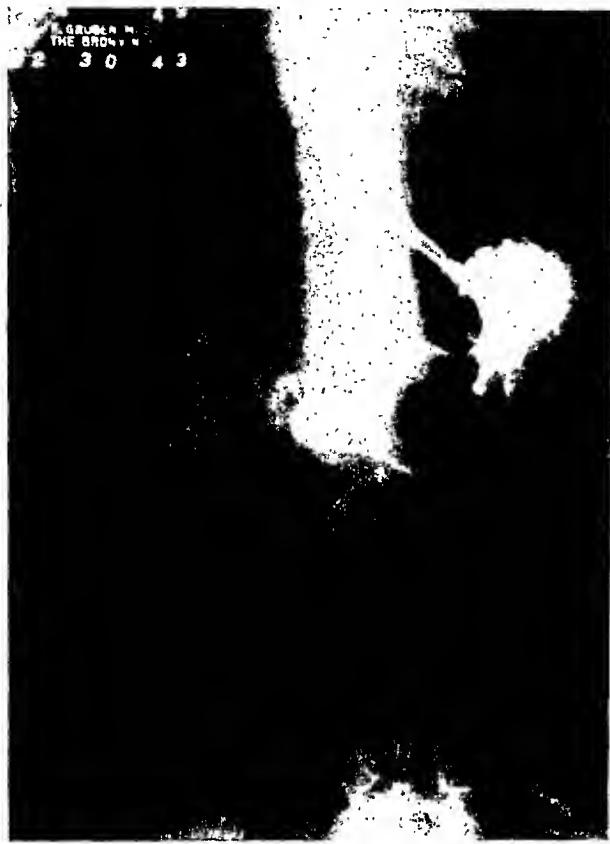


Figure 3. Constriction of the corpus at the borderline of its two segments. The mid-gastric sphincter according to Aschoff and Stieve.

isthmus-like contraction divides the stomach into an upper part composed of the fornix (fundus) and upper part of the body, and a lower part composed of the

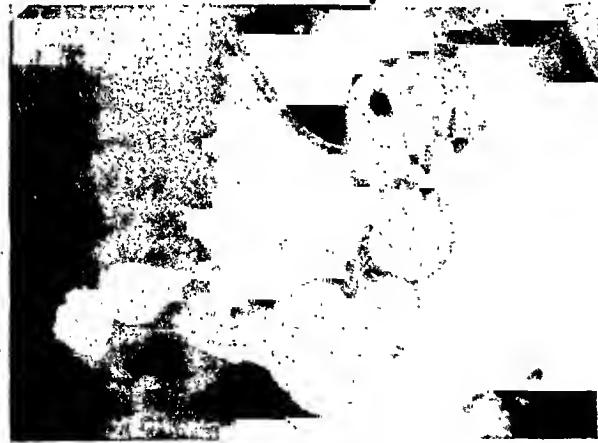


Figure 4. Anatomical division of the stomach. Segmentation of the corpus and pars pylorica.

vestibulum or the rest of the body and the canalis pylori. The mid-gastric sphincter was seen also by Stieve⁶ in 1919 when he examined the stomachs of persons immediately after execution.

Cannon⁷ observed by means of his bismuth feeding and x-ray method that a similar contraction took place in animals during normal digestion. Hertz⁸, by the same method, established the fact that a similar constriction was to be observed during normal digestion in man. He noted that the constriction may proceed to such a depth as to completely separate the antrum pylori from the fundic part of the stomach. Groedel⁹, on the basis of careful radiological studies, described the pre-pyloric sphincter in man and considered it to be an anatomically pre-formed structure. Martin and Rogers¹⁰, after introducing balloons into the human stomach



Figure 5. Segmentation of the fundus of the stomach.

and inflating them, observed on the silhouette of their roentgenograms a complete circular constriction in the lower third of the stomach.

My intention was to study the anatomy of the human stomach and the influence of a localized mechanical stimulus on the motility of the different parts of the stomach. For this purpose I¹¹ had to apply a new method which consisted of introducing balloons into the fasting stomach, followed by the administration of barium suspension and the registration of the phenomena on roentgenograms. I used three different kinds of balloons: 1) a large balloon made of reinforced latex finger cot which, when inflated, was ovoid in shape; 2) a small balloon made of the closed end part of a finger cot, ball-shaped when inflated; 3) a balloon made of a piece of Penrose tubing, $\frac{1}{4}$ inch wide, crescent (sausage)-shaped when inflated. The balloons were attached with a strong silk thread to the buckle of a Rehfuss

tube. I used three different kinds of tubes: 1) a tube made of pure gum, non radio-opaque material; 2) the regular Rehfuss tube, semi radio-opaque; 3) a double

Their studies were on hunger contractions and were conducted with double balloons. A small balloon was placed within a larger one and an emulsion of bismuth and vaseline introduced between their walls. Martin and Rogers¹⁰ introduced single balloons into the human stomach without the application of a radio-opaque substance either inside the balloon or the stomach. Their interest also lay in a study of hunger contractions.

The results which I obtained with my method were as follows:¹¹ I was able to produce transverse constrictions at the borderline of the different parts and segments of the human stomach. (Fig. 1-2 and 3). I



Figure 6. A complete filling of the stomach with barium meal and without the balloon. Demonstration of the stomach as a transport system.

tube, i.e., a connected pure gum and Levine tube. The balloon in this case was attached to the buckle of the pure gum tube, whereas the Levine tube was used only



Figure 7. Same stomach as in Figure 6. A small balloon is inflated with 30 c.c. of air in the pars pylorica. Observe the haustral segmentation. Demonstration of the stomach as a digestive system.

to withdraw contents from the stomach or eventually to introduce fluids into it.

Rogers and Hardt¹² in 1915, were the first to introduce balloons into the human stomach for x-ray studies.



Figure 8. Systolic contraction of the pars pylorica after inflating a small balloon with only 30 c.c. of air.

observed the subdivision of the human stomach into three different parts which as functional unities are connected with each other anatomically as well as physiologically. These parts are the fundus, the corpus or body, and the pars pylorica. These parts could be further divided into subdivisions (segments). It could be proven that a rhythmic segmentation (as in the intestines) exists in the human stomach. (Fig. 4 and 5). The subdivision of the body and pars pylorica could be observed not only by the transverse folds separating them from each other but also by the different phases which existed in the different segments. The phases of the segments in the body of the stomach were inverse to those observed in the pars pylorica. In the body there was a proximal dilatation and a distal contraction, while in the pars pylorica a proximal contraction and a distal dilatation took place. As to the segmentation of the different parts of the stomach, only the pars

pylorica has been known to be subdivided into segments. According to His¹³ the pars pylorica is subdivided by muscular contractions into three parts: the camera



Figure 9. Inertia of the muscles of the pars pylorica and consequently atonia of the pars pylorica due to the inflation of a large balloon with 1200 c.c. of air in the fundus and body of the stomach.

princeps, the camera minor, and the camera tertia. Because of the inconstancy of the muscular contractions, His suggested dividing the pars pylorica into the vesti-

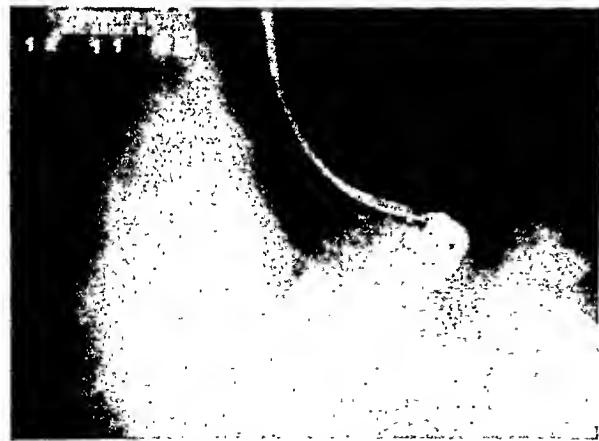


Figure 10. The pyloric sphincter was kept open and the duodenal bulb distended by the inflated balloon. The pars pylorica is in a systolic phase while the body is in a diastolic phase.

bulum pyloricum and canalis pyloricus, as described by Jonesco and Erik Mueller.

Knowledge of the anatomy of the stomach is the key to radiological interpretation of the many variations of

its form. By this is meant not only the descriptive anatomy of the organ but also the physiological anatomy, since the wall of the stomach is formed of strong muscular coats and the contraction or relaxation and, in certain instances, the inertia of these muscles are responsible for the constant changes.

The radiologists must take into consideration the two main functions of the stomach, or rather of the gastro-intestinal system: that of serving as a transport system, and the other of serving as a chemical plant. It is well known that in fulfilling these two functions the muscles of the stomach play a very important role. Not only to



Figure 11. Two inflated balloons in the duodenum (one in the bulb the other in the descendent part of the duodenum). Relaxation of the body and pars pylorica of the stomach is present.

convey its content from one segment to the other, but also in order to exert its chemical function, the stomach must contract powerfully around the ingested food. The entire gastro-intestinal system serves these two purposes (except the esophagus, which serves only a carrying purpose; under normal circumstances food does not remain there). According to these functions will the shape and size of the stomach and intestines change. The form of the stomach will also change according to the internal or external abdominal pressure, the position of the patient, the respiratory movements, and the stage of filling.

The routine barium meal examination reveals the fundamental changes of the stomach which are characteristic of its function as a transport system but very little of those which characterize it as a digestive organ, since water or watery suspensions quickly leave the

stomach. There is no doubt that contractions of the stomach are different when meat, eggs, etc., are ingested. How differently the stomach appears after a barium meal ingestion and after eating solid food can be imagined if I show the x-rays of a man whose stomach was radiographed after receiving only the regular barium meal and when a small balloon was inflated in the pars pylorica. In the first instance (with the stomach completely filled with the barium meal) all the compartments are confluent with each other; there is no segmentation of the stomach. The contractions serve to convey the contents of the stomach into



Figure 12. The balloon was inflated in the body of the stomach and produced the contraction of the oblique muscle of the stomach. See also Figure 2, which is the same man's stomach.

the intestines. In the second instance (in the same subject), when a small balloon is inflated in the first segment of the pars pylorica, the similarity of the stomach to the large bowel is very striking. There is a real haustral segmentation of the stomach. In this case, the contraction of the stomach serves the purpose of digestion. (Fig. 6 and 7).

The most amazing feature in my experiment was the systolic contraction of the entire pars pylorica. The pars pylorica which contracted around the small balloon inflated with 30 c.c. of air not only became narrower in its transverse diameter but also shorter in its longitudinal diameter. This could not occur unless both the circular and the longitudinal muscles of the pars pylorica had contracted simultaneously. (Fig. 8). In order to produce a systolic contraction of the pars pylorica, the balloon had always to be in the first segment of the

pars pylorica beyond the incisura angularis. The inflation of a small balloon with 30 c.c. of air was enough to cause the entire pars pylorica to contract around the inflated balloon, although in certain cases even 80 c.c. of air produced only the contraction of the first segment of the pars pylorica. I was never able to produce the systolic contraction of the pars pylorica when the balloon was inflated in the second (caudad) segment, although in two cases 200 c.c. of air were inflated.

To draw a contrast between the pars pylorica in the state of contraction and in that of inertia, I shall describe the behavior of the stomach when the balloon



Figure 13. The balloon was inflated in the second segment of the pars pylorica. Three exposures were made (polygram). There is a contraction of the longitudinal muscle present (the stomach is crescent shaped). Observe the pendular movement of the longitudinal muscle. No circular muscle contraction is present. (This is the same stomach as in Figures 12 and 2).

was impacted in the fundus and body of the stomach. In proportion to the amount of air blown into the balloon the pars pylorica became relaxed step by step. When there were only 800 c.c. of air in the balloon a simple relaxation of the circular and longitudinal muscles took place in the pars pylorica, and as the amount of air in the balloon increased to 1200 c.c. the relaxation of the muscles became even greater and finally reached a state of inertia. This was evident by the change of the shape and tonus of the stomach as it clearly appeared on the films taken with the patient in a standing and postero-anterior position and also in an antero-posterior position. (Fig. 9). This change in tonus and shape of the stomach may be due to the inertia of the muscles in the pars pylorica consequent to stimulation in the fundus and body of the

stomach. Pfaundler¹⁴ found, by means of gastrodiaphany, that the stomach increases in volume after lavages of the stomach, and that this increase in



Figure 14. Crescent shaped balloon was inflated in the body of the stomach but not sufficiently to produce a contraction of the circular muscle. Observe the contraction of the circular muscle appearing as shallow traveling waves. (3 exposures were made, polygram).

volume is due to an inertia or paralysis of the muscles of the stomach. Pfaundler calls that condition hypotony due to lavage or gastro-paresis after lavage.



Figure 15. (Same stomach as in Figure 14). The balloon was inflated sufficiently to produce a contraction of the circular muscle around the balloon. Polygram shows only a pendular movement of the longitudinal muscle.

As to the behavior of the stomach when the pyloric sphincter is kept open and the duodenal bulb distended by the inflated balloon, observations on animals



Figure 16. Routine barium meal X-ray shows an ulcer in the pre-pyloric region on the lesser curvature side of the stomach.



Figure 17. Same stomach as in Figure 16. A small balloon inflated with 30 c.c. of air contracted only the first segment of the pars pylorica. (See also Figure 1, which is the same stomach.)

(Wheelon and Thomas¹⁵) confirm my observation that the pars pylorica in a systolic condition is strongly contracted and shortened, while the body in a diastolic phase is relaxed. (Fig. 10).

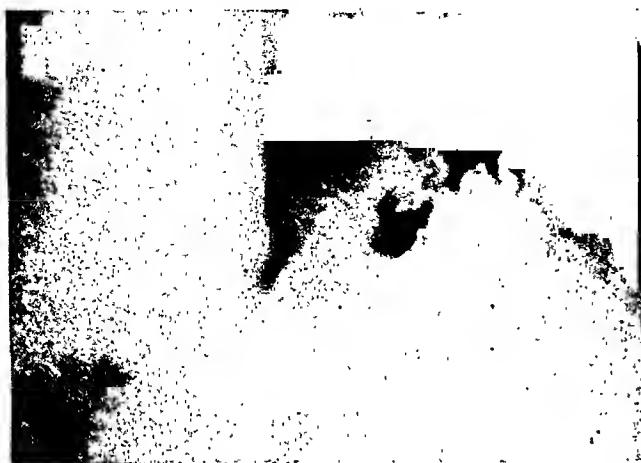


Figure 18. Regular barium meal X-ray of the stomach shows the incomplete filling of the stomach on its lesser curvature side.

When the duodenum was distended by the inflated balloon and the pyloric sphincter was constricted, a relaxation of the body as well as of the pars pylorica was observed. (Fig. 11). According to Tobler¹⁶, who distended the duodenum with a balloon in animals, this distention brings about an inhibition of gastric motor activity.

I have introduced balloons and inflated them in the duodenal bulb and in the following segments of the



Figure 19. Same stomach as in Figure 18. A large balloon was inflated in the fundus and corpus of the stomach. The pars pylorica became even more relaxed.

duodenum in nine patients. I did not observe the irradiation of autonomic reflexes in the sense of Bruno Kisch¹⁷, resulting in tachycardia, pallor, sweating and nausea, except in one case which I have described¹¹.

As to the function of the three muscle layers of the stomach, my observation is as follows:

The oblique muscle, which is continuous to the circular muscle fibers of the esophagus, forms a sling (Forssell¹⁸) from the esophagus down either side of the lesser curvature. I observed the contraction of this muscle when the balloon was located beneath the incisura angularis and inflated, and when the balloon was

inflated in the body of the stomach; its contraction shortens the stomach above the incisura angularis on the lesser curvature side. When this muscle contracts, the body of the stomach assumes a perpendicular position, while the pars pylorica remains in a horizontal position. (Fig. 12; see also Fig. 2). Consequently, an angle of almost 90 degrees will be present at the incisura angularis although in some instances I observed an angle smaller than 90 degrees. When the oblique muscle is relaxed and the longitudinal muscle contracted, the entire lesser curvature is concave and the stomach is crescent-shaped. A lesion on the lesser cur-

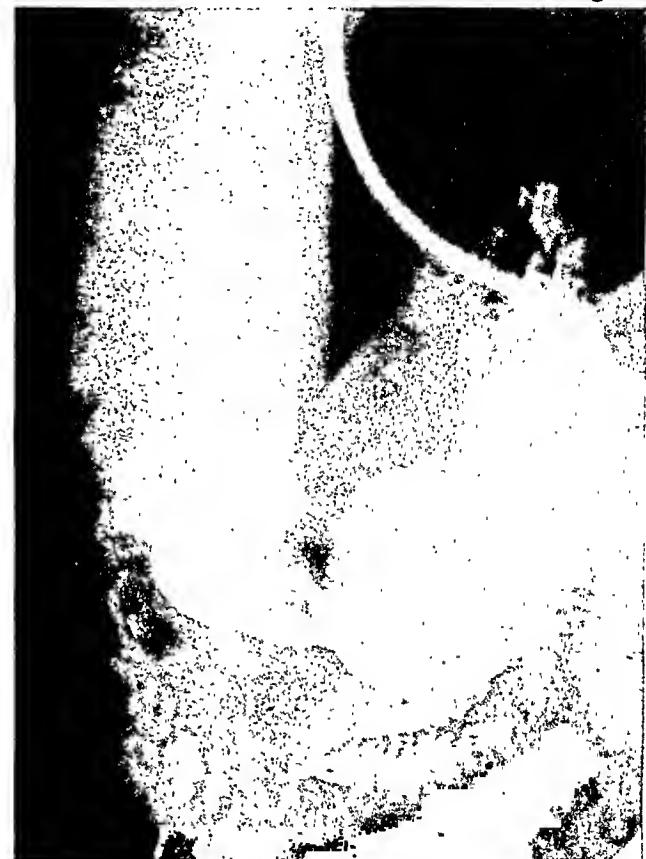


Figure 20. Same stomach as in Figures 18 and 19. A small balloon inflated in the pars pylorica produced the systolic contraction of this part of the stomach.

vature at or above the incisura angularis may cause the contraction of the oblique muscle and consequently the change in form of the stomach described above.

I found constrictions due to sphincter-like contractions of the circular muscle of the stomach at the borderlines of the different parts and segments of the stomach. By sphincter-like contractions I mean that the circular muscle is able to contract like a sphincter, not that the muscle is a real sphincter, since anatomically this was not proven. The circular muscle can contract over a part or segment of the stomach, entirely obliterating that part or segment. It may contract in successive waves along the stomach forming salients and indentations. Finally, it may contract simultaneously with the longitudinal muscle, and then a systolic phase will be present at the given part or segment of the stomach.

When the longitudinal muscle contracts the stomach

becomes shorter. This muscle may contract all along the stomach, or along a part or segment only. According to Toldt¹⁹ the longitudinal muscle fibers enter the pyloric sphincter and divide it into several bundles. In



Figure 21. A regular X-ray investigation shows a fillings defect in the pre-pyloric region on the greater curvature side of the stomach.

this way he considered that the longitudinal fibers may act as a dilator of the pylorus. Forsell¹⁸ believes that the circular muscle is in intimate connection not only with the ligamenta ventriculi but also with the entire longitudinal muscle. No part of the longitudinal muscle can be detached without cutting apart the muscle layer lying beneath the longitudinal layer, that is, the circular muscle. This intimate connection of the longitudinal and circular muscles apparently enables the longitudinal muscle to act like a sphincter dilator all along the stomach. When the longitudinal muscle is contracted over a part or all of the stomach, there will be no sphincter-like contraction of the circular muscle in any part of the stomach. I was able to produce contractions of the longitudinal muscle all along the stomach and to inhibit the motility of the circular muscle when I inflated the balloon in the duodenum and the second segment (caudad segment) of the pars pylorica. This I could prove by polygrams which distinctly show a complete standstill of the circular muscle while there was a pendular movement of the longitudinal muscle all along the stomach. (Fig. 13). To inhibit the motility of the circular muscle a contraction of the muscle around the inflated balloon seems to be necessary. This I observed when I inflated the balloon in the body of the stomach not sufficiently to produce the contraction of the circular muscle around the inflated balloon. Under such circumstances I observed contractions of the circu-

lar muscle appearing as shallow traveling waves along the body and pars pylorica of the stomach. There were no sphincter-like contractions under these conditions in the body and pars pylorica. (Fig. 14 and 15).

I have studied the human stomach with this balloon method in 44 cases and now I am applying the method for diagnostic purposes. My procedure consists of the routine x-ray examination of the stomach and the x-ray examination of the stomach with the aid of the balloon, the latter performed in combination with the Rehfuss test meal. I introduce double tubes, one a Levine tube, the other a Rehfuss tube. The balloon is attached to the buckle of the Rehfuss tube. The Levine tube serves the purpose of withdrawing the stomach contents. After the fractional test meal the stomach is completely emptied by aspiration and the barium meal is given to the patient to drink or else the barium suspension is injected through the Levine tube into the stomach, if the patient is disturbed by nausea or vomiting. This is followed by the inflation of the balloon and the x-ray examination.

To show the diagnostic value of this method I will describe the case of a 45 year old woman. Previous examinations showed no abnormalities in her stomach or duodenum. With the inflation of a crescent-shaped balloon I could detect an ulcer crater on the lesser curva-



Figure 22. Same stomach as in Figure 21. A small balloon inflated in the first segment of the pars pylorica did not produce the systolic contraction of this part of the stomach. Observe the fillings defects in the pre-pyloric region on the lesser and greater curvature sides.

ture of the stomach near the incisura angularis. I was able also to produce an hourglass contraction of the stomach. (See: Fig. 4). In x-rays taken only with the regular barium meal method the stomach has the shape

of the one described when the oblique muscle is contracted; that is, the body of the stomach is in a perpendicular position while the pars pylorica is in a horizontal one. The lesion on the lesser curvature is responsible for this form of the stomach.



Figure 23. Routine X-ray of a cascade stomach with malignant infiltration of the corpus. (Upright postero-anterior position.)

In the case of a 49 year old man, the regular barium meal x-ray studies showed an ulcer on the lesser curvature of the stomach in the second segment of the pars pylorica. (Fig. 16). After the introduction and inflation of a small balloon in the first segment of the pars pylorica, with only 30 c.c. of air, I could produce only a contraction of the first segment of the pars pylorica. At the borderline between the first and second segments of the pars pylorica a marked transverse contraction of the circular muscle took place. There was also an apparently strong contraction in the second segment of the pars pylorica, which was responsible for the very distinct visualization of the ulcer on the lesser curvature side of this segment. (Fig. 17). It is important to note that a further inflation of the balloon with more than 30 c.c. of air was impossible because of the severe pain of which the patient complained when I tried to inflate more air in the balloon. The balloon was inflated also in the second segment of the pars pylorica and here I could not inject more than 25 c.c. of air because of the severe pain which the patient again experienced while I was manipulating in this segment. A kind of "défense musculaire" takes place and inhibits the inflation of the balloon with a larger amount of air. (See: Fig. 1).

As to the diagnostic value of this method in malignant lesions or to clear up doubtful conditions such as

filling defects (due to a mass in the stomach) or inertia of the muscles, the following three cases are very instructive:

1. The first case was that of a 50 year old man who had been treated for an ulcer of the duodenum for four years. I saw him two years prior to this examination, when x-rays of the stomach and duodenum showed a duodenal ulcer pocket on the lesser curvature side. This time the patient had an attack of severe pain and constant vomiting which started one week prior to the examination. The routine x-ray examination showed the ulcer pocket in the duodenum. A remarkable finding was the relaxation of the muscles of the stomach and duodenum. The muscles at the lesser curvature side were relaxed to such a degree that I could not get a filling of that side. This incomplete filling appeared as a filling defect and salients (Haudek) characteristic in malignancy of the stomach. (Fig. 18). After this finding I introduced and inflated a large balloon in the body and fundus of the stomach. (This was at the beginning of my experiments, when I introduced and inflated only large balloons). I thought that by inflating the balloon I would push the barium meal into the pars pylorica and so fill up that part with barium completely. But the more air I inflated in the balloon the



Figure 24. Same stomach as in Figure 23. Patient is in an upright left oblique postero-anterior position. Observe the fundus showing only a liquid level.

more relaxed the pars pylorica became and the more the signs of incomplete filling appeared. (Fig. 19). At this stage I was about to report to the wife of the patient that her husband had a cancer of the stomach.

Two days later, in another case and for the first time, I succeeded in contracting the pars pylorica around a balloon inflated with 30 c.c. of air and in bringing this part of the stomach into a systolic phase. I was able to produce that systolic contraction of the pars pylorica



Figure 25. Same stomach as in Figures 23 and 24. Same position as in Figure 24. Balloon inflated in the fundus of the stomach shows the extension of the lesion into this part of the stomach.

in the case just described; the man with the duodenal ulcer and relaxation of the muscles of the stomach and so to make it clear that only the muscular relaxation and the crinkles of the rugae on the lesser curvature were responsible for the filling defect and salients which appeared on the first x-rays. (Fig. 20).

2. In the case of a 60 year old man, the routine x-ray investigation showed a filling defect in the second segment of the pars pylorica. (Fig. 21). After the introduction of a small balloon into the first segment of the pars pylorica beyond the incisura angularis and repeated inflation of the balloon with 50 to 150 c.c. of air, no

systolic contraction of the pars pylorica could be produced. However, contractions of the circular as well as the longitudinal muscle could be produced up to the infiltrated area of the pars pylorica, thus distinctly separating the intact part of the stomach from the malignantly infiltrated prepyloric region. (Fig. 22).

3. Finally, the case of a 57 year old man should be mentioned. The routine barium meal x-ray method showed a cascade stomach with malignant infiltration of the body, manifested by filling defects on the lesser and greater curvature sides of the stomach. With the balloon method the infiltration of the fundus also could be detected, giving a real picture of the extent of the lesion. (Fig. 23, 24 and 25).

SUMMARY

A method of introducing balloons into the fasting human stomach and duodenum, followed by the administration of barium suspension, is described as a means of producing mechanical stimulation in the different parts and segments of the stomach and duodenum and of studying the behavior of the stomach, its anatomy and motility, and the eventual detection of an organic lesion by means of the x-ray.

Application of this method proved the following facts:

1. The stomach is divided into three separate parts which, as functional units, are connected with each other anatomically as well as physiologically. These three parts are the fundus, the corpus (or body) and the pars pylorica.

2. The fundus, the corpus, and the pars pylorica are further divided into subdivisions (segments).

3. There is a rhythmic segmentation in the stomach similar to that in the intestines.

4. Transverse constrictions could be produced at the borderline of the different parts and segments of the stomach.

5. Complete contraction of the pyloric part of the stomach could be produced, proving that the circular as well as the longitudinal muscles of this part of the stomach contracted simultaneously, and this part of the stomach was brought to a systolic phase while in the body of the stomach the circular and longitudinal muscles remained relaxed (diastolic phase).

6. The motility of the three muscles of the stomach could be studied.

7. The balloon method serves as a diagnostic aid in determining the presence of an organic lesion (ulcer or malignant infiltration) in the stomach.

REFERENCES

1. Cruveilhier, J.: Traite d'anatomie descriptive Tome III, page 276, 1843.
2. Froriep, A.: Uber Form und Lage des menschlichen Magen. Verhandl. der Ges Deutscher Naturforsch. u. Arzte, 78 Vers. zu Stuttgart. 16-22 Sept. 1906, Second Part—page 313.
3. Schindler, R.: Gastroscopic Observation Concerned with the Gross Anatomy of the Stomach. The Musculus Sphincter Antri; Observation of the Position of the Stomach; The Mucosal Folds. Am. J. of Dig. Dis. and Nutr., 1936-7; 3: p. 149-153.
4. Wepfer: Cited from Cathcart, The Prepyloric Sphincter. The J. of Physiol., 1911: vol. 42: p. 93-106.
5. Aschoff, L.: Uber den Engpass des Magens (Isthmus Ventriculi) 1918; Verlag Gustav Fisher Jena.
6. Stieve, H.: Der sphincter antri pylori des Menschlichen Magens. Anat. Anz., 1918-19; 51: 513-534.
7. Cannon, W. B.: The Movement of the Stomach Studied by Means of the Roentgen Rays, Am. J. Physiol. 1898; I: p. 359-382.
8. Hertz, A. F.: The Passage of Food through the Human Alimentary Canal. British Med. J., 1908; p. 130-137.
9. Groedel, F. M.: a) Die Magenbewegungen. Fortschritte auf dem Gebiete der Rontgenstrahlen Ergänzungsband, 27, p. 198, 1912. b) Cited from Alvarez Int. Gastro-Ent. p. 291-293.

10. Martin, C. L. and Rogers, F. T.: Hunger Pain. Am. J. of Roe, 1927; 17: p. 222-227.
11. Gruber, F.: A New Method of Studying the Anatomy and Motility of the Stomach and Duodenum, Experimental Medicine and Surgery, Volume II, No. 1, February, 1944; p. 1-35.
12. Rogers, F. T., and Hardt, L. L. J.: Contributions to the Physiology of the Stomach, Am. J. Physiol. 1915; 38: 274-84.
13. His, W.: Studies an gehäerteten Leichen über Form und Lagerung D. Menschlichen Magens. Arch. f. Anat. u. Entw. 1903; p. 345.
14. Pfaundler, M.: Über Magen kapazität und Gastrectasie im Kindesalter. Bibliotheca Medica, Abt. d. H 5. Stuttgart 1898.
15. Wheelon, H., and Thomas, J. E.: Observations on the motility of the duodenum and the relation of the duodenal activity to the pars pylorica. Ann. J. Physiol. 1922; 59: 27-96.
16. Tobler, L.: Über die Eiweiss Verdauung im Magen. Zeitschrift f. Physiol. Chemie, 1905; 45: p. 185-215.
17. Kisch, Bruno: 38 Kong. D. Ges. Innere Med. 1926; p. 153. Zsch. F.d. ges exp. Med. 52, 1926; p. 999. Vier Vorlesungen über Kreislauffragen by Dr. Bruno Kisch. Verlag Paul Kuschbert, Kohn, 1934.
18. Forssell, G.: Über die Beziehung der Rontgenbilder des menschlichen Magens zu seinem anatomischen Bau. Fortschritte auf dem Gebiete der Rontgen Strahlen Ergänzungs vol. 30. Page 167. Hamburg Lucas Grafe & Silliem 1913.
19. Toldt: Cited from Schinz, H. R., Baensch, W., und Friedel, E. Lehrbuch der Roentgen Diagnostik, 1928, Second Ed., Georg Thieme Verlag Leipzig, p. 841.

Common Features of Chronic Amoebic Colitis

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ALTHOUGH it is now a well established fact that most of the patients with amoebic infection of the large bowel present a picture which resembles any chronic low-grade infectious colitis, with correlated manifestations which involve reflex and toxic phenomena, principally related to the gastro-intestinal tract and the nervous system, a great number of physicians continue to think of amoebiasis in terms of acute dysenteric episodes. This is particularly true with those practitioners not too familiar with digestive problems and with those who work in regions where amoebiasis is not very widespread or is not yet recognized as a common affection.

As a matter of fact, this protozoosis cannot be regarded any more as an exclusively tropical disease, notwithstanding its prevalence in hot and temperate climates. After the Chicago epidemic outburst of amoebiasis, in 1933, the incidence of this protozoa has been studied with increasing interest all through the United States and figures as high as 42 per cent of certain whole communities, or groups have been found by Faust (1, 2), in New Orleans, among 4,000 examined individuals.

Johnstone, David and Reed (3), examining the feces of 1,000, just after admission to the California State Prison, disclosed 92 carriers of Endamoeba histolytica. Sumerlin (4) reports an incidence of 2.1 per cent, among 1,336 private patients, and Tsuychia and T. Jean (5) found 12 carriers (2.3 per cent) of cysts of *E. histolytica*, among 562 freshman medical and dental students, at the Washington University, St. Louis, Missouri.

Even in the northern parts of the United States, infection with amoeba dysenteriae is not an uncommon finding. Epidemiologic investigations, carried out by the Board of Health of Chicago (6), revealed as many

as 100 persons presenting *E. histolytica* in the stools out of 498 examined (20.0 per cent). Among 364 food handlers, 26 (7.1 per cent) were infected with this protozoa, as shown by the same inquiry. As far as we now know, the coldest regions in the world do not seem protected by their constant low temperature against this parasite invasion. Epstein (7) reports an incidence of 25.3 per cent amoeba carriers, among 1,404 examined habitants of Leningrad, Russia, and in the Kola Peninsula, entirely situated within the Arctic Circle, there were 60 per cent carriers out of 900 individuals. We must not forget it was in Saint Petersburg, that Loesch, in 1875, first isolated the Endamoeba histolytica from the feces of a dysenteric patient. T. Wight and V. Wight (8) demonstrated the cysts of *E. histolytica* can stand a 7° Centigrade temperature as long as 46 days. Craig (9, 10), who has thoroughly dealt with problems of endoemic amoebiasis, estimates that somewhere from 5 to 10 per cent of the whole population of the United States harbor this parasite.

In South America, as far as we know, epidemiologic studies have been carried on in Argentina and Brazil. Large investigations performed in that former country by Castex and Greenway (11, 12), displayed a proportion of 18.8 per cent, out of 2,771 individuals, with *E. histolytica* in the stools. In Brazil, its frequency seems to vary from 8.33 (Renault and Versiani, 13), up to 15.2 (Moniz de Aragao, 14) and even 40.0 per cent (Amaral, 15) in certain parts of the country. In a statistical study, concerning ward patients of a General Hospital (Santa Casa da Misericordia), in Rio de Janeiro, we found 14.0 per cent harboring amoebae dysenteriae. These 65 patients, examined so far, sought hospital care for circulatory, respiratory, urologic or nervous afflictions or on account of digestive diseases others than dysentery.

With the continuous dislocation of considerable masses of people, brought about by present world

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circumstances, it may be expected that many regions, so far relatively spared, will see their statistical figures of amoebiasis and other so-called tropical diseases notably increase. As far as the United States is concerned, this is not a remote possibility after the return of the troops now scattered in so many tropical and near tropical regions such as South America, the Philippines, India, Africa and the Mediterranean Basin. A deeper knowledge will then be required on the part of American physicians in order to deal with the common as well as with the unusual aspects of several diseases contracted in those areas. In this paper, it is our purpose to stress some of the most common features of chronic amoebic colitis on the bases of two of our recent cases. A more thorough study of the subject was attempted by us, with Dr. Velho da Silva (16), in a previous publication.

Case 1. Miss M. G., a white woman, 45 years old, resorted to medical advice for mild epigastric pains, not related to meals, pyrosis and acid regurgitations for several years. She also complained of difficulty in digesting fat foods, such as fried eggs, omelette, pork, ham and pastry. She stated "she was constipated since she was a girl" and her bowels often didn't move for as long as 8 days and sometimes 10 days. Usually she was able to get a bowel movement only with the help of enemas or cathartics. There were other minor symptoms such as nervousness, occasional headaches, backaches, moderate asthenia, weak legs and occasional pains on the calves. These latter disturbances increased during the menopause period. Previous menstrual history was normal. Two years ago, menses stopped rather suddenly, to return after one year's interruption. Menses disappeared again about four months ago. She felt more nervous and had frequent hot flashes at this time.

Physical examination revealed a well nourished, moderately obese woman, of a rather florid complexion, 60 inches tall and weighing 137 pounds. Examination of the abdomen, the first time we saw the patient, revealed only discrete tenderness over the epigastric region and on the right lower quadrant. Other systems were negative.

Radiologic studies of stomach and duodenum failed to show any evidence of organic or functional alterations. Gastric analysis demonstrated moderate hyperchlorhydria (Ewald's test). Gallbladder exploration, both by x-ray and duodenal intubation (Meltzer-Lyon's test), reported slow emptying, without evidence of stones or inflammatory involvement of bile ducts. The patient was put on a soft fiber, low fat, low protein diet and she was given colloidal aluminium hydroxyde as well as gallbladder stimulants. Some duodenal intubations were performed, aiming at the restoration of gallbladder motor function. Gastric symptoms gradually subsided and after two months she complained but little of pyrosis and gastric pains. Constipation, however, persisted almost as obstinate as ever. We examined her again and again and noticed definite tenderness on both lower quadrants, as well as under the right costal margin. The descending colon appeared palpable, contracted and moderately tender. She failed to recall any previous dysentery or severe diarrhea, but com-

plained of diffuse abdominal colic and marked meteorism. Sigmoidoscopy revealed a fairly extensive amoebic ulcerative colitis, involving all the portions of the sigmoid colon which could be seen through the scope. Remarkable improvement followed anti-amoebic therapy, carried out with emetin hydrochloride, enterovioform and carbarsone. General digestive disturbances notably improved and the patient began to have a bowel movement every two days, without the use of enemas or cathartics. She discontinued treatment for a few weeks and constipation increased again, although not so obstinate as it formerly was. Under a new course of acetarsone, the patient started to move her bowels daily. She still is under treatment.

This observation, like several others, illustrates the frequent occurrence of constipation as the outstanding and sometimes almost sole colonic disturbance induced by amoebic infection of the large bowel. In many patients, more or less protracted periods of constipation are punctuated by outbreaks of mild or severe diarrhea. Some others have diarrhea or dysentery only at the onset of their disease. From then on, after the first attack is controlled, but the amoebae not entirely eradicated as the treatment was insufficient, they become constipated. It is not uncommon for the patient to have forgotten that first manifestation and it is up to the physician, by minute questioning, to recall this initial episode and so date back the onset of the disease.

Based on the analysis of 2,700 cases of chronic amoebiasis, Castex and Greenway (12) state that "in their statistics, constipation has been the outstanding functional disturbance of the colon, sometimes in a moderate degree, but not infrequently of a very tenacious and obstinate character. Among 600 French soldiers with amoebic colitis, of whom many had contracted the disease during World War I, Hillemand and Martinier (17) noted 23 who never presented dysentery or diarrhea. Constipation was the only trouble with their bowel. Two of these constipated patients had vegetative forms of *E. histolytica* in the stools. As has been pointed out by J. T. Howard (18), this is not an unusual discomfort associated with the so-called amoeba carriers. These are persons, without striking symptoms of disease, in whom an epidemiologic survey discloses the presence of *E. histolytica* in the feces. In the investigation of cyst carriers examined, in a Rio de Janeiro General Hospital, this appeared to be quite true. S. Simon (19) claims that fairly extensive lesions are found to occur along the intestinal tract without producing any impressive manifestation or positive evidence of their presence. The same statement is made by Hiyeda and Suzuki, on the basis of their experimental work (20). Simon says that "at least 50 per cent of the individuals, who harbor pathogenic amoebae, never become recognizant of the presence of the organisms within the body." This group of so-called symptomless or healthy carriers, nevertheless, usually displays some ill effects and various general and nervous disturbances which may be traced for the most part to the presence of a particularly obstinate form of constipation, a condition which is quite common during the less active phases of amoebiasis.

On the other hand, it is necessary to consider the cases with partial constipation which may mislead even the most expert clinician. Although the patient states he moves his bowel every day, this evacuation is scant and incomplete. This may be explained by the marked spasticity of the large bowel (21), which leaves behind it a true fecal residue, particularly at the cecum and terminal ileum. As a result of the roentgenologic study of several cases of amoebic colitis, J. Bell (22) demonstrated as a constant feature, the existence of pronounced narrowing of the cecum, sometimes cone shaped or assuming the aspect of a small pouch with almost complete obstruction of the cecal lumen. Besides this, Bell noticed, as a frequent finding, incompetence of the ileocecal valve, allowing the barium to regurgitate into the terminal portion of the small bowel without any appreciable obstacle.

In spite of our emphasizing the significance of constipation as one of the most constant symptoms of chronic amoebiasis, we do not want to infer that it is the only colonic disturbance. Not to speak of spontaneous or elicited pain and meteorism, in many patients the concurrence of diarrhea and even dysenteric episodes may be observed. These, however, occur at variable intervals of several months, and usually they appear on a background of habitual constipation.

Diarrheic outbreaks commonly consist of two to four liquid evacuations with or without noticeable mucus and may or may not be accompanied by colics. They may be called forth by certain foods, emotions, fatigue or another incident disease. Sometimes it occurs without any definite cause. Without proper fecal and proctoscopic examination, these manifestations may be mistaken for food allergy, allergic colitis, unstable colon or functional neurosis. Provided these patients with ulcerations or even simple catharral lesions of the colonic wall are prone to present kaleidoscopic general and sympathetic disturbances, we have heard that latter diagnosis not infrequently made. It is possible that the influence of some foods, in promoting diarrheic attacks, may be explained on the bases of the modification of the intestinal flora. This can happen as a result of germs carried by the food itself or on account of chemical alterations of the intestinal contents, favouring or inhibiting the development of bacteria within the bowel lumen. The experimental work of Chinn et al. (23) showed the importance of bacterial flora on the cultivation of *E. histolytica*.

Another question deserving further discussion, in chronic intestinal amoebiasis, is that of spontaneous pain and tenderness induced by manual palpation. This may be observed on any portion of the large bowel tract, but seems more frequent on the cecal area and over the ascending colon. Not rarely it also shows itself on the sigmoid colon. Among 600 patients with amoebic colitis, Hinman and Kampmeier (24) remarked spontaneous diffuse abdominal pains 92 times. Thirteen had pain only over the right lower quadrant and five others on the left lower quadrant. Twenty-one patients complained of epigastric pain. Upon physical examination, 169 of the patients in that series were found to have

abdominal tenderness on a circumscribed region. In the majority, it appeared to spread all over the abdomen. Of the former, in 32 patients the pain was situated exclusively on the right lower quadrant and 25 others referred it to the right upper quadrant. This predominance of painful phenomena in the right abdomen appears clear enough when one recalls the distribution of amoebic lesions, which, as a rule, predominate on the cecum and ascending colon. Anatomic studies by Clark (25) and Faust (2), as well as the experimental work of Kessel (26), among others, particularly pointed out this location. It is not hard to figure out then how easily this tenderness on the right abdomen, induced by large bowel lesions, may lead one to suspect gallbladder disease or chronic appendicitis. The following case constitutes an example of the clinical problems above mentioned.

Case 2. A. H., a white, married male, 29 years old, engineer, from Salvador, State of Bahia, stated he has been suffering the last 5 years from mild epigastric pains, not definitely related to meals. Usually, however, the pains became worse with a fasting stomach and improved after taking food. Pyrosis, flatulence and gas have been common complaints throughout this time. He feels worse with a too fatty diet, as well as with acid fruits. His bowel moves every day, but it seems this daily evacuation is rather deficient, consisting of a small volume of stools. There are occasional diarrheas. One physician advised appendectomy, which was performed 3 years ago, but he failed to improve after operation. Two other physicians, consulted afterwards, diagnosed gallbladder disease, put him on a low fat diet and gave him biliary antiseptics and sedatives. This brought him some relief, but his suffering always recurred. On careful interrogation, the patient traced these morbid manifestations back to a first and severe attack of diarrhea he had, 5 years ago, when travelling in the inland of the State of Bahia. He says, however, he didn't lose appreciable weight, although he became very "temperamental," easily irritated, getting upset by trifling events. Many times he feels dizzy and has a quite unpleasant sensation of cold hands and perspiration in the palmar regions. Past history is irrelevant, but for primary syphilitic infection 4 years ago. He followed complete anti-luetic therapy courses.

Physical examination shows a strongly built, well-nourished individual, 63 inches tall and weighing 180 pounds. Normal tension of abdominal wall. Normal Traube's space. Mild tenderness over the epigastrium. Liver within normal limits. Definite tenderness on palpation of the right hypochondrium and on both right and left lower quadrants. We were able to palpate a spastic and tender sigmoid and descending colon. Physical examination otherwise negative, except for mild chronic bronchitis, with some rales, sibilant in character, on the lower half of the right hemithorax. Blood pressure, 140 systolic, 80 diastolic. Pulse rate 93 a minute. During examination, the patient looked easily excitable, talking exuberantly, describing his continued suffering and the inferiority complex it was creating for him. He became tired easily, was unable to work hard

and often awoke in the morning with a feeling of fatigue as if he hadn't had enough rest. Fecal examination of one loose stool showed several vegetative and cystic forms of *Endamoeba histolytica*. Sigmoidoscopy was performed next day. The scope was introduced without difficulty up to 15 cm. Above this point, the sigmoid colon was spastic, hardly allowing the instrument to pass. Several small ulcerations were seen at this level. The ulcers looked whitish in appearance, covered with mucus. All the mucosa was paler than normal, with adherent mucus. Rectal ampulla and rectal canal appeared normal.

The patient was prescribed a soft fiber diet, vitamin B complex and alternate courses of emetine hydrochloride, iodochlorohydroxyquinoline (enteroform) and carbarsone. He felt definitely better one month after the beginning of this treatment. Pyrosis and epigastric pain completely subsided. Two months later he still had occasional tenderness on the right abdomen. He particularly stresses that, soon after the onset of the medication, the volume of stools notably increased. However he continues to move his bowel once a day. He had two or three semi-liquid defecation only once thereafter. Psychic status is much better and he now is working hard in the construction of an airfield, almost 12 hours per day, with renewed energy.

The first point, deserving mention in the above observation, is the resemblance of the history and clinical findings to the picture of many chronic gallbladder processes with chronic appendicitis. In fact, this patient was diagnosed chronic cholecystitis by two different physicians and had his appendix out, after three years' illness, without any noticeable improvement. The prevalence of amoebic lesions on the ascending colon and eventually on the right half of the transverse colon constitutes sufficient explanation for the pain over the so-called gallbladder area (27). This doesn't exclude the possible coexistence of a true amoebic cholecystitis, which although a rather rare occurrence, has been proved by the finding of pathogenic amoebae in the surgically removed gall bladder (Petzetakis, 28) and by its presence in the vesicular bile obtained through duodenal intubation (Boyers and Kofoid, 29, Almeida Prado, 30).

The involvement of the cecum, almost usual in amoebiasis, accounts for the not rare clinical confusion with chronic appendicitis. As a matter of fact, the protozoa itself can originate a real acute appendicular inflammatory process so acute and as urgently calling for surgical therapy as the most genuine acute appendicitis of any other etiology, as has been shown in publications by Craig (9), Brown (31), Harrison (32), Runyan (33), Hogan (34) and as we also have found. Sometimes a previous history of dysentery or the fortunate occurrence of diarrhea, shortly after the onset of acute phenomena such as sharp pains and fever, accompanied by abdominal rigidity and leukocytosis, may lead to a fecal examination which then affords the key for correct diagnosis. Only medical treatment after surgery can assure complete healing of these cases.

Another aspect deserving emphasis is the multiplicity

of sympathetic and general disturbances the patients with chronic amoebiasis are prone to present. Symptoms like palpitation, tachycardia, feeling of cold extremities, unpleasant palmar perspiration (35), vasomotor manifestations, erythemas and several dermatoses, epigastric discomfort, backache, particularly at the lumbosacral region, headache, nervousness, anguish, fatigue and "nervous breakdown" are not unusual complaints with these patients. Some of them will probably depend on a chronic enterogenous auto-intoxication. Hypersecretion of mucus by the inflamed mucosa and fecal stasis can favour the multiplication of certain bacteria and so modify the normal large bowel flora, leading to abnormal processes of fermentation or putrefaction of the intestinal contents. Moreover, the lesion of the intestinal mucosa itself may permit the absorption of these pathologic products and antigens, thus causing the toxic and allergic manifestations. The sympathetic system plays then a major role in such a sensitized organism (Trabaud, 36). Actually, many patients with chronic amoebic colitis present a clinical syndrome quite similar to that of the really functional unstable colon or to the gastro-intestinal disturbances of dystonic and nervous individuals with the so-called mucous or membranous colitis. Toxic substances elaborated in the inflamed walls of the large bowel represent in such circumstances effective stimuli for these sympathetic reflexes which may spread themselves on the gastro-intestinal tract itself, the skin, the circulatory system or on the nervous system as a whole. These may occur as short-circuit reflexes, involving two contiguous or nearby segments of the bowel and then promote spasm, gaseous distension, borborygmus and pain. At other times they may have the wide range of long distance reflexes, projecting their effects principally on the whole gastro-intestinal tract and on the circulatory system. Almeida Prado, from Sao Paulo, reported an illustrative observation, concerning a physician who presented impressive attacks of palpitation, cold sweating, vomiting and lipotimia so severe as to cause him to fall down. This patient lost about 24 pounds and reached a miserable status of mental asthenia, and suffered from cardiophobia. Amoebae were found by duodenal intubation and he was cured with anti-amoebic therapy. In fact, these circulatory phenomena look very similar to those we have seen in some patients with chronic enterocolitis and cholecystitis caused by *Giardia Lamblia*.

As stated by James and Deeks (37), we must learn to recognize such reflex manifestations of chronic amoebic colitis as accurately as we recognize those of chronic appendicitis. We have to agree, however, that in a few cases the clinical picture is so puzzling and intestinal disturbances so inconspicuous that diagnosis of amoebiasis could hardly be made by history or physical examination (38). Peculiar tenderness on the right or left lower quadrants, a previous episode of dysentery or diarrhea may then help the expert clinician, suggesting the need of adequate complementary investigation and so put him on the right track. This is particularly true with patients who dwell in tropical areas.

DIAGNOSIS

Diagnosis of chronic as well as of acute amoebic colitis rests principally on proper stool examination. This ought to be performed in freshly passed feces, after a saline administration, looking for vegetative forms of the parasite and in regular stools, with some enrichment technic, for cysts. We have had satisfactory results with Faust's zinc-centrifugal flotation method. As Sawitz and Faust (39) pointed out, at least 4 successive examinations, combining direct and concentration technic, are necessary in order to rule out, with 90 per cent of accuracy, the existence of amoebic infection.

Sigmoidoscopy and examination of material collected through the scope may prove itself the only diagnostic resource in a few cases. Diagnostic value of endoscopic exploration, however, should not be over-estimated, owing to the greater incidence of amoebic lesions on the right colon. Even when the distal colon is involved, pathological alterations, as seen by sigmoidoscopy, may not display any characteristic features. Among the 600 cases of chronic amoebic colitis, reviewed by Hilman and Martinier, already quoted, there were 44.8 per cent with normal looking mucosa (17). In the remaining 55.2 per cent, proctoscopic findings varied from simple congestion (21.6 per cent), pinpoint hemorrhages and vascular dilatation (16.6) and congestive hemorrhagic lesions of the mucosa (11.0) to small ulcerations covered with mucus (1.6). Only a few (0.3 per cent) presented deep ulcers on the rectal mucosa. Studying a series of 115 patients with amoebic dysentery, seen at the Mayo Clinic, Jackman and Cooper (40) noticed ulcerative lesions of the lower part of the bowel in only 20.8 per cent. In two of those cases, biopsy and scrapings of the ulcers, collected through the proctoscope, afforded the unique diagnostic resource, as repeated examinations of stools had given negative results.

Radiology, although very helpful in showing the site and extension of the large bowel involvement, ought always to be associated with the aforementioned meth-

ods of complementary investigation in order to afford an etiological diagnosis.

In some patients who present a suspicious clinical history and findings, anti-amoebic therapy should be attempted, even when fecal and proctoscopic examinations are negative. Its striking results afford convincing evidence of the correctness of the clinical assumption.

TREATMENT

Healing of chronic amoebic colitis is principally a question of long and sustained use of specific drugs. We have treated some patients for more than 6 months before they could be judged free of the protozoal infection long harbored by the colonic walls. Castex (41) states its cure may take even more than two years to completely eradicate the parasite. It is our routine practice to prescribe alternate courses of iodochlorohydroxyquinoline (enteroviosform), 0.25 gram, 3 to 5 times a day, for 10 to 20 days and pentavalent arsenicals: acetarsone (stovarsol) or carbarsone, 0.25 gram, twice a day, for 10 days. During the first course of enteroviosform or carbarsone, emetine hydrochloride is usually associated: 0.04, daily, for 15 days. Yatren is also useful in doses of 0.25 gram, 2 to 6 times a day, orally or given with small enemas (1 to 2 per cent aqueous solution, 100 c.c.). Manifestations of intestinal irritation, however, are common with this latter drug and we have the impression enteroviosform is perhaps more active and surely better tolerated. Soft fiber diet, sedatives, antispasmodics and vitamin B complex, as a rule, go on with specific therapy.

In certain cases it is necessary to periodically renew the course of one of the anti-amoebic preparations, as some of the symptoms may recur, milder but still present. They give proof of the remarkable resistance acquired by the protozoa after a long stay within the body and call for the repetition of specific therapy which will be well rewarded for being as tenacious as the parasite itself.

REFERENCES

1. Faust, E. C.: The distribution and diagnosis of amebic enteritis in the Southern United States, New Orleans Med. Surg. Jour., 86: 605, March, 1934.
2. ibd.: Amebiasis in New Orleans population as revealed by autopsy examination of accident cases, The Am. Jour. Trop. Med., 21: 35, Jan., 1941.
3. Johnstone, H. G., David, N. A. and Reed, A. C.: A protozoal survey of one thousand prisoners, J.A.M.A., 100: 728, March, 1933.
4. Sumerlin, H. S.: Amebiasis, incidence in private practice, J.A.M.A., 102: 363, Feb., 1934.
5. Tsuchiya, H. and Jean, J. T.: The incidence of intestinal protozoa among freshman medical and dental students with special reference to amebiasis, The Am. Jour. Trop. Med., 20: 803, Nov., 1940.
6. Bundesen, H.: Amebic dysenteric epidemic in Chicago, Am. Jour. Digest. Dis. and Nutrition, 1: 9, March, 1934.
7. Epstein: Trop. Dis. Bulletin, April, 1934.
8. Wight, T. and Wight, V.: On the viability of cysts of Endamoeba histolytica under variable conditions, The Am. Jour. Trop. Med., 12: 581, Sept., 1932.
9. Craig, C.: Amebiasis and Amebic dysentery, A. Jour. Digest. Dis. and Nutrition, 1: 4, March, 1934.
10. ibd.: The epidemiology of amebiasis, J.A.M.A., 103: 1091, Oct., 1934.
11. Castex, M. and Greenway, D.: Sobre parasitosis intestinal, Arch. Argent. enf. ap. digest. y de la nutricion, 3: 276, 1928.
12. ibd.: Consideraciones parasitologicas y clinicas sobre 2700 casos de amebiasis intestinal, Prensa Med. Argent., 21: 2049, Oct. 1934.
13. Renault, L. and Verian, W.: Parasitismo humano por helmintos e protozoarios em Belo-Horizonte, Brasil-Med., 54: 487, July, 1940.
14. Moniz de Aragão, R.: Febre typhoide, dysenterias e diphtheria em Joao Pessoa, Brasil-Med., 52: 1058, Nov., 1938.
15. Franco do Amaral, A.: Healthy carriers of Endamoeba histolytica, J.A.M.A., 123: 650, Nov., 1943.
16. Vello da Silva, J. J. and Lopes Pontes, J. P.: Amebiasis intestinal nao dysenterica, An. Santa Casa de Misericordia, Rio de Janeiro, 1: 60, 1944.
17. Hillenbrand, P. and Martinier, L.: L'amebiasis au Centre de Reforme de Paris, Presse Med., no 52: p. 104, July, 1939.
18. Howard, J. T.: The clinical significance of the Carrier

- state in Amebiasis. *The Am. Jour. Digest. Dis.*, 6: 506, Oct., 1939.
19. Simon, S.: The clinical diagnosis of Amebiasis, *J.A.M.A.*, 103: 1063, Oct., 1934.
20. Hiyeda, J., and Suzuki, M.: Pathological studies of human amoebic ulcers, specially those of carriers, *The Am. Jour. of Hyg.*, 15: 809, May, 1932.
21. Vallarino, J. J.: Preliminary report on the value of the roentgen ray in estimating the extent of amebic infection of the large intestine, *The Am. Jour. of Trop. Med.*, 5: 149, March, 1925.
22. Bell, J. C.: Roentgenologic studies of the large infection in infections by *Endamoeba histolytica* before, during and after treatment, *The Am. Jour. of Roentgenol.*, 39: 918, June, 1938.
23. Chin, B. et all.: The influence of the bacterial flora on the cultivation of *Endamoeba histolytica*, *The Am. Jour. of Trop. Med.*, 22: 137, March, 1942.
24. Hinman, H., and Kampmeier, R.: Clinical intestinal amebiasis, *The Am. Jour. of Trop. Med.*, 17: 263, March, 1937.
25. Clark, : The distribution and complications of amebic lesions found in 185 post-mortem examinations, *The Am. Jour. Trop. Med.*, 5: 157, 1925.
26. Kessell, J.: Amoebiasis in kittens infected with amoebae from acute and carrier human cases and with tetrancysteate amoebae of the monkey and pig, *The Am. Jour. of Hyg.*, 8: 311, May, 1928.
27. Simon, S.: The clinical aspects of amebiasis, *New Orleans Med. Surg. Jour.*, 87: 355, Dec., 1934.
28. Petzidakis, M.: De la realite de la cholecystite amibienne. *Ann. de Med.*, 26: 66, July, 1929.
29. Boyers, L. M., Kofoid, C., and Swezi, O.: Chronic human amebiasis, *J.A.M.A.*, 85: 1441, Nov., 1925.
30. Almeida Prado, A.: Concepcao pathogenica e tratamento da amebiase intestinal, *Rev. de Biol. e Med.*, 1: 16, Jan., 1940.
31. Brown, P.: Certain atypical types of amebiasis, *Am. Jour. Digest. Dis. and Nutrition*, 1: 10, March, 1934.
32. Harridon, W.: The histopathology of appendiceal amebiasis with case report, *Ann. of Inter. Med.*, 2: 1081, April, 1929.
33. Runyan, R. W.: Surgical complications and treatment of intestinal amebiasis, *The Am. Jour. of Trop. Med.*, 5: 137, March, 1925.
34. Hogan, E. P.: Appendicitis caused by *Endamoeba histolytica*, *J.A.M.A.*, 75: 727, Sept., 1920.
35. Craig, C. F.: Clinical aspects of amebiasis, *New Orleans Med. Surg. Jour.*, 86: 609, March, 1934.
36. Trabaud, M. J.: Amebiase et systeme vago-sympatique, *Bull. de l'Academie de Med.*, 11: 142, Jan., 1934.
37. James, W. M., and Deeks, W. E.: The etiology, symptomatology and treatment of intestinal amebiasis, *The Am. Jour. of Trop. Med.*, 5: 97, 1925.
38. Goyena, J. R.: Los pclifros de la amebiasis latente, *An. de Inst. Modelo de Clin. Med. Buenos Aires*, 21: 154, 1940.
39. Sawitz, W. G., and Faust, E. C.: The probability of detecting intestinal protozoa by successive stool examinations, *The Am. Jour. of Trop. Med.*, 22: 131, March, 1942.
40. Jackman, R. J., and Cooper, W. L.: Value of proctoscopy in the diagnosis of amebiasis. *The Am. Jour. of Digest. Dis.*, 10: 365, Oct., 1943.
41. Castex, M.: La clinica de la amebiasis, *Prensa Med. Argent.*, 26: 1347, July, 1939.

The Action of Ketocholanic Acids Upon Lower Bowel Motility

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WHOLE bile, the bile acids and their salts have been used mainly to promote the functions which these compounds perform under physiological conditions. Chief among these are the roles played in certain digestive processes, most particularly the emulsification and the absorption of fats and fat soluble accessory substances, vitamins A (including carotene), D and the anti-hemorrhagic K.

Of the compounds derived from bile, the bile acids are the most effective and their outstanding pharmacological action is their choleric effect. The bile acids under certain conditions, seem to promote bowel motility and hence have been recommended as cathartic agents. Their efficacy in this respect has remained undecided although it is well known that in large amounts they quite regularly induce diarrhoea.

Data on the results of local application of bile compounds to the various parts of the intestinal tract are meagre. It seemed of interest to investigate the effects

of the rectal administration of certain bile salts of known composition. We have conducted such a study in animals and man, and desire in this communication to report our observations.

The use of bile compounds to promote emptying of the lower bowel can be traced back to the ancients, who applied oxgall mixed with honey rectally to induce defecation. For generations, animal bile in the form of enemata has been a favorite home remedy.

In 1866 Leyden (1) observed diarrhoea in rabbits following rectal administration of a solution of bile acids. In 1907 Hallion and Nepper (2) noted that bile acids administered rectally in dogs resulted in defecation. Similar effects were obtained by Glaessner and Singer (3) who followed the same procedure in both animals and man.

The data herein detailed were obtained from observations on rabbits and man. The preparation used was a 20% w/v mixture of sodium ketocholanate*, consisting principally of sodium dehydrocholate and sodium dehydrodesoxycholate in the same relative proportion as they exist in whole bile.

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ANIMAL EXPERIMENTS

Eleven rabbits were used. Three were anaesthetized with sodium pentobarbital solution intravenously. A median abdominal incision was made exposing the intestinal loops. The field of operation was isolated by means of a cellophane membrane thus permitting observation of the behavior of the abdominal viscera without exposing the organs to cooling and drying. By means of a small rubber tube attached to a syringe, 5 ml. of the sodium ketoconolate solution was introduced into the rectum and the behavior of the lower bowel observed. After a latent period of about 30 seconds, a sudden increase in activity was noted in the lower sigmoid and in the rectum, resulting after about four to seven minutes in copious fecal evacuations. The bowel movements were invariably preceded by rhythmic contractions of the anus. The small and the remainder of the large intestine did not take part in the peristaltic activity.

tally instead of the drug. Seven did not react to this placebo but the three which had slight bowel evacuations were excluded from further studies.

Usually no symptom was noted during the first few minutes after administration. Later, in some cases, a sensation described as hot, cold or itching appeared. Three to six minutes after the fluid was injected, periodic rumblings in the left upper abdomen was experienced. Peristaltic movements became evident and gave way to pressure in the suprapubic region. About five minutes later the first sign of pressure in the perineum was felt, which increased in intensity and resulted in a strong desire to defecate. If the patient was able to resist the impulse and postponed defecation for two or three minutes when the tenesmus would reach its peak, a much better defecation resulted, than if he evacuated with the first sensation.

The movements were less satisfactory in those cases which had been constipated for a number of days and

TABLE I
Action of Sodium Ketoconolate on Rabbits By Rectal Administration Within a 45 Minute Period

Animal No.	Weight in lbs.	Volume of drug in ml.	Time of action (min.)	Experimental Period		Control Period	
				Number of Stools	Amount of Stools (gm.)	Number of Stools	Amount of Stools (gm.)
1	6	2	5	4	4.7	0	0
2	7	2	9	2	8.0	0	0
3	8	2	5	1	3.3	0	0
4	8	2	5	1	3.5	0	0
5	10	2	4	1	0.75	0	0
6	10½	2	7	6	8.5	0	0
7	7	2	3	5	6.4	1	0.4
8	7	2	17	3	1.7	?	5.0
8*	7	5	2	3	3.9	0	0

Time of action indicates time elapsed between administration and first bowel movement.

Control period gives the data collected within a 45 minute period, 24 hours after the experimental period. No drug was administered preceding the control period.

* In this animal an additional amount of the drug (5 ml.) was administered because of the somewhat delayed action after the first administration of 2 ml.

Eight additional intact rabbits were given 2 ml. of the sodium ketoconolate solution in the identical manner described above. The number and weight of the fecal movements were noted during a 45-minute period following the rectal injection. The frequency of evacuation and the amounts of evacuated material were increased as compared with a control period of the same duration, at the same time the following day, when no medication was given before or after the interval of observation (See Table I).

CLINICAL EXPERIMENTS

A group of 61 patients with a variety of diseases (chiefly cardiovascular disturbances) were given 105 injections per rectum in a manner similar to that used in the rabbits. Each dose contained 5 ml. or 10 ml. of the sodium ketoconolate solution. In addition, in half the number of cases rectal suppositories of 2 gram total weight containing 1 gram of sodium ketoconolate in a cocoa-butter base were used in place of the rectal injections. In 10 cases 10 ml. of water was given rec-

in which the stool was hard and dry. A repetition of the rectal installation succeeded in producing a satisfactory movement. Repeated administration did not produce any local irritation. Burning sensation was complained of in about 15 per cent of the patients.

TABLE II
Effect of Sodium Ketoconolate in 105 Administrations To 61 Patients

Material Administered	No. of Trials	Results		
		Good	Moderate	None
		No. Percent	No. Percent	No. Percent
5 ml. 20% Sodium Ketoconolate	22	10 45.4	5 22.7	7 31.8
10 ml. 20% Sodium Ketoconolate	60	33 55.	10 16.7	17 28.3
Suppository containing 1 gm. of Sodium Ketoconolate	23	13 56.5	4 17.3	6 25.8

Where suppositories were used the effect and the sensations were identical, but the evacuation was slightly delayed. The frequency of burning was much greater than from the solution, about half of the subjects having noticed it. Untoward reactions or bitter taste were not noted by any of the subjects. The fact that the time between administration and reaction was so constant and of such short duration led us to believe that possibly there is a central reflex mechanism involved in the process (See Table II).

The delayed action of the suppository is probably due

TABLE III
*Time Elapsed Between Administration and Action
Of Sodium Ketocholanate in 105 Administrations*

Time of Action	SOLUTION		SUPPOSITORy	
	5 ml. (1 gm.)	10 ml. (2 gm.)	1 gm.	
Within 8 minutes	4	18.1	14	23.3
8 - 15 minutes	8	36.3	14	23.3
15 - 20 minutes	1	4.5	4	6.6
After 20 minutes	2	9.0	11	18.3
No effect	7	31.8	17	28.3
TOTAL	22	60	23	

REFERENCES

1. Leyden, E. Beitrag. Z. Path. des Icterus Berlin, 1866.
2. Hallion, L., and Nepper, H.: Influence Existmotorice de la Bile sur l' intestine. Compt. rend. de la soc. Biol. 63, 182, 1907.

to the fact that some time must elapse before it melts and releases the contained bile salts.

Our experience indicates that the combination of bile salts used here is especially suited in cases of rectal constipation particularly when the expulsive power is inadequate. It should be helpful after barium enemas and gastro-intestinal studies where remnants of contrast material sometimes remain in the recto-sigmoid and cause intractable constipation.

Further clinical investigations are planned to study the use of the sodium ketocholanate solution and the suppository as an adjunct in situations in which prompt rectal emptying is required but in which large quantities of fluid are objectionable, i.e., proctoscopic manipulation, operative procedures on the rectum and in preparation for obstetric delivery. It might be of value as an aid in roentgenographic visualization of the gastro-intestinal tract, where peristalsis is desired for observation.

SUMMARY

A preparation of sodium ketocholanate was studied for its effect upon lower bowel emptying in rabbit and in man. Administered into the rectum in the form of solution in 5 or 10 ml. quantities, or as a suppository it produces regularly, after a short latent period, copious defecation. Suggestions for its use are described.

Book Reviews

Duodenal and Jejunal Peptic Ulcer. Technic of Resection. By Rudolf Nissen. Foreword by O. H. Wangensteen. Pp. 143, 123 illustrations (\$4.75). Grune and Stratton, Inc. New York 16, N. Y. 1945.

Although the title of the monograph emphasizes the operative technic, the clinical problems of the ulcer disease are concisely discussed. Of particular value are the author's observations on the etiology, since he was able to observe an impressively vast number of ulcer patients of different races, of very divergent psychologic background as well as disparate dietetic and nutritional habits.

While his approach to the treatment of gastric and duodenal ulcer is rather conservative, he gives a sensible explanation of the rationale of the surgical therapy, which—as it is now accepted—is gastro-duodenal resection whenever possible. Here is the point where questions of operative technic come into play. It is the author's opinion that subtotal gastrectomy in gastric ulcer (*sensu strictiori*) is well standardized, its mortality being negligible. The gastroenterologist will agree with the author that the situation is different in duodenal ulcer. The radical procedure here is still weighed with a comparatively high risk. That is partic-

ularly true for the perforating group of duodenal ulcers which present the vast majority of peptic ulcers requiring operation. To be more precise, the danger point here is the closure of the duodenal stump, for the leakage of the stump is the main reason for mortality in these cases. The author has developed a particular kind of duodenal resection and closure, its steps being thoroughly described and pictured.

Over a period of twelve years, the experiences obtained from many hundreds of operations are definitely encouraging, as is the fact that the author's principle has been adopted by Roscoe Graham, Wangensteen, Von Haberer and other surgeons known for their achievements in ulcer surgery.

General application of a radical procedure in duodenal ulcers would help to replace the exclusion resection where, as is well known, ulcer, pylorus, and a considerable part of the antrum are left behind. Gastroenterologists have never been much in favor of this operation mainly on account of the high postoperative morbidity, as evident from reports published by some of our leading clinics.

The less experienced surgeon will welcome the chapter dealing with technical mistakes occurring on the

operating table as, for instance, too extensive resection of the duodenum which does not permit closure of the stump by inversion.

With regard to the group of non-perforating duodenal ulcers, the author is in favor of the Billroth 1 procedure. Wangensteen, in his foreword, lends support to this opinion on the basis of animal experiments. A technic of the Billroth 1 method, where certain technical shortcomings are avoided, is explained and illustrated.

Another major chapter is devoted to the technic of resection of postoperative gastro-jejunal ulcers and gastro-jejunal colic fistulas. Particular emphasis is placed on the experience that in marginal ulcers any operation short of radical resection, is useless. This opinion apparently is shared by most surgeons today.

The procedures indicated according to the different possible locations of the postoperative gastro-jejunal ulcer are described in the light of complicated anatomic conditions that may be encountered.

For poor risk patients—certainly the majority of patients requiring operation—a two stage operation is recommended and illustrated.

The value of a book like this depends largely on the quality of the illustrations. There are 123 drawings—most of them dealing with technical maneuvers pictured step by step. It may be said that these pictures are really excellent, serving their purpose in a perfect manner.

Annual Review of Physiology Vol. VI, 1944. Edit. by J. M. Luck and V. E. Hall. Pp. 630 (\$5.00). Stanford University P. O., Calif., Annual Reviews, Inc., 1944.

Since 1939 there has appeared annually a review of the year's periodic literature in physiology. Each chapter covers a particular subject and is written on invitation of the Editorial Board by men known to have specialized in the particular field under review. The literature covered consists mainly of non-clinical papers in pure and applied physiology. However clinical papers are also reviewed when these contribute something of importance to the understanding of normal and pathologic functions.

The present volume has kept the high standards of the preceding numbers. Nineteen chapters, on as many topics, are devoted to reviewing over 3200 papers, most of which appeared in medical and biological journals between July 1942 and July 1943. The subjects reviewed range from Developmental Physiology and the Physiology of Neoplastic Growth to Physiological Psychology and Industrial Physiology. Of particular interest to the internist will be the reviews on Tissue Water and Electrolytes by D. C. Darrow (covering 133 journal papers), Energy Metabolism by M. Kleiber (125 papers), Respiration by T. Benethal (126 papers), Digestive System by B. Slutsky and A. C. Anderson (131 papers), Liver and Bile by L. A.

Crandall Jr. (78 papers), Blood by A. J. Quick (235 papers), Heart by R. Ashman (179 papers), Visceral Functions by B. A. McSwiney (115 papers) and Metabolic Functions by F. G. Young (401 papers).

These Annual Reviews have proved of extreme value not only to the physiologist but also to all who wish to keep abreast of recent advances in those branches of the medical sciences which are basic to their own specialties. This volume is heartily recommended to the general practitioner, specialist and physiologist alike.

The Chemistry and Pharmacy of Vegetable Drugs. By Noel L. Allport. Pp. 252 (\$4.50), Brooklyn, N. Y., The Chemical Publishing Co., Inc.

Here is a well illustrated review of vegetable drugs, including the important alkaloids, diuretics, carminatives, rubefacients, expectorants, anti-helminthics and flavoring and coloring agents. Methods of preparation, tests for purity, various forms for administration and interesting descriptions of the sources and commercial states are given in almost each instance. The author points out that the use of vegetable drugs probably never will be discontinued, and cites penicillin as an unexpected "find" from the vegetable kingdom, from which others may be expected to emerge. While it is true that hormones and vitamins have accomplished good results, we are properly reminded that a good prescriber can still obtain excellent effects from the use of a wide range of vegetable drugs. The book is stimulating and up-to-the minute.

Essentials of Allergy. By Leo H. Criepp, M.D., Pp. 381 (\$5.00), Philadelphia, J. B. Lippincott Company.

In a comparatively small, well tabulated, well-illustrated book the author provides all that an internist ordinarily needs for the intelligent understanding and treatment of hypersensitivity. The treatise is pre-eminently practical and very little space is devoted to theorization. The reviewer was struck by the author's conservatism, so plainly seen in his refusal to adopt "promotional" attitudes or to accept extreme positions. He obviously realizes that allergy will receive serious consideration at the hands of the practitioner more willingly when the subject is presented with restraint, rather than as an explanation of all disease. This is fortunate because of the public's attitude. Today "allergy" ranks with "sinus" and "colitis" as popular maladies and the physician becomes inclined to disregard many of the aspects of allergy, even in instances where careful investigation would lead to fruitful clinical findings. Criepp has passed over gastro-intestinal allergy somewhat too briefly but refers to Rowe's work and presents some useful elimination diets.

Any practitioner resolving to do better justice to the allergic phases of practice than he has done in the past would be well-advised to buy this book first, for it describes all essential techniques and provides tables of doses and geographic distribution of allergins.

Abstracts of Current Literature

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CLINICAL MEDICINE

STOMACH

SCHIFF, L., SHAPIRO, N., AND BLOCH, H. S.: *Gastric excretion of sulfadiazine in man. Observations on normals, patients with peptic ulcers, atrophic gastritis, and gastric cancer.* (*J. Clin. Invest.*, v. 23, p. 946, Nov., 1944).

Five grams of sodium sulfadiazine were administered intravenously and the concentration of the drug was determined in the blood and in the gastric juice of each of the 43 patients.

The concentration of sulfadiazine in gastric juice of patients with gastric cancer and achlorhydria was found to be higher than in normal persons, patients with gastric or duodenal ulcer, or with atrophic gastritis either with or without achlorhydria.—B. R. Adolph, Jr.

BOWEL

FALLIS, J. S.: *Regional enteritis.* (*Med. Record*, v. 38, p. 862, Sept., 1944).

There are three stages of regional enteritis and the patient may show one of the three. Stage I, the acute or appendicular stage, usually leads to a diagnosis of appendicitis because of the pain, vomiting, nausea and leukocytosis. Usually the terminal ileum is involved. Stage II, the subacute ulcerative or irritative stage, shows ulceration of the mucosa and stools containing much mucus. Intestinal hemorrhage is uncommon. Stage III, the chronic or obstructive stage, shows symptoms of partial intestinal obstruction. Complete obstruction is infrequent. The thickened intestinal wall may be palpated and is sometimes mistaken for an abscess or malignancy of the digestive tract. Fistulas in all three stages are common; they are intractable and palliative measures are without benefit. Operative treatment should be performed only in the quiescent stage. If operation for appendicitis is undertaken and stage I is found, the appendix should not be removed because of the danger of fistula formation. Resections of the segments of bowel are possible but only if they do not involve diffuse areas but are limited.—B. R. Adolph, Jr.

HAXTON, H. A.: *Hernia of caecum into lesser sac of peritoneum complicated by volvulus.* (*Brit. Med. J.*, No. 4380, p. 729, Dec. 16, 1944).

Only about 50 cases of intestinal herniation through the opening into the lesser sac of peritoneum have been

presented in the literature since the first description in 1834. In only ten cases was the cecum present in the lesser sac and in no case was volvulus reported present. The case described is therefore unique in this respect. Probably herniation was present for some time but was not suspected until the volvulus was superimposed giving rise to symptoms of strangulated intestinal obstruction.—F. E. St. George.

HOWAT, H. T.: *Fatty diarrhoea in chronic and relapsing dysentery.* (*Lancet*, v. 247, p. 560, 1944).

Five cases are quoted of fatty diarrhoea supervening in the course of chronic or relapsing dysentery. Inadequate diet, diarrhoea, or use of sulfaguanidine may result in a B-complex deficiency, the former by reduced intake, the two latter by reduced synthesis in the intestine. Steatorrhoea may also result from the same cause.—Biological Abstract.

COSTA, A., AND ROMERO, H.: *Bacillary dysentery in childhood.* (*Rev. chilena pediat.*, v. 14, p. 905, Dec., 1943).

One hundred and thirty-two children in a group of 618 ill children examined presented clinical evidence of enterocolitis. Dysentery organisms were isolated in 22 per cent of the enterocolitis cases. Positive cultures were obtained in only two of the 488 sick children that served as controls. The clinical features of dysentery are discussed.—A. S. Martinez.

ESPIRITO, J. J., AND STOUT, A. P.: *Multiple plasmacytoma of the jejunum.* (*Am. J. Roentg. Rad. Therap.*, v. 53, p. 33).

Plasmacytoma may occur in any part of the body, but less commonly outside bone marrow. Symptoms are hemorrhage (melena), dull pain in upper and lower left side of abdomen which is unrelated to food, nausea and anorexia. Roentgenograms show the lower jejunum to have lost its mucosal pattern and to be constricted. There may be the suggestion of an ulcer. In the case cited operation and pathological examination revealed a plasmacytoma. The patient died of intestinal obstruction one year post operative.—Wm. S. Snape.

PANCREAS

HOWARD, P. J.: *Familial character of fibrocystic disease of the pancreas.* (*Amer. J. Dis. Child.*, v. 68, p. 330, Nov., 1944).

There are at least twelve instances recorded in the literature of familial occurrence of fibrocystic pancreatic disease. The present case is an addition to these twelve. Three patients, two sisters and one brother, had fibrocystic disease of the pancreas. Three brothers, all apparently free of the disease, survive.—John J. Cox.

LIVER AND GALLBLADDER

VOLAVSKY, W.: *Dermatoses and metabolic functions of the liver.* (*Arch. Dermatol. Syph.*, v. 184, p. 268, 1943).

Liver function tests, including the galactose and glycine tests, were performed on 100 patients with various types of dermatoses. Among the patients were those with chronic eczema, lichen urticatus and neurodermatitis. Definite disturbances in liver function were found in a high percentage of these cases. It is believed that both the dermatoses and the liver dysfunction are due to a pathologic process which is common to both and it is therefore suggested that the whole form a pathogenetic unit.—G. Kleuner.

AMBERG, S., AND ZUSCHLAG, E.: *Congenital biliary obstruction.* (*Proceed. Staff Meet. Mayo Clinic*, v. 19, p. 570, Dec. 13, 1944).

The most common cause of biliary obstruction is a congenital anomaly. Among 5395 necropsies, 20 cases of abnormalities were found. Diagnosis was established either by surgical exploration or post mortem examination. Biliary obstruction may be suspected when, in the first weeks of life, the patient is jaundiced, has acholic stools, deeply colored urine, hepatomegaly and splenomegaly. While only a few cases are amenable to surgical treatment, the authors point out that the sooner surgical treatment is accomplished, the better is the chance that the liver can recover from the damage caused by the obstruction. Surgical treatment was aimed at establishing a connection between bile ducts or the gall bladder and the duodenum or stomach. However, the gall bladder in some cases was small, rudimentary or absent, or else embedded in the liver. In cases where the patient is an adult, drainage from the liver to the outside has been recommended. Most statistics indicate, however, that the majority of cases of infants with anomalies of the biliary tract die before the age of 6 months.—R. L. Burdick.

BOYDEN, E. A., AND LAYNE, J. A.: *Evacuation of the gall bladder in female patients with pernicious anemia.* (*Proceed. Soc. Exper. Biol. Med.*, v. 57, p. 315, Dec., 1944).

The study includes 48 consecutive unselected cases of pernicious anemia, comprising 23 men and 25 women. Gall bladder visualization was absent in 35 per cent of the males and 48 per cent of the females. Necropsy records of 105 pernicious anemia patients showed that 32.4 per cent had had cholelithiasis or cholecystitis, or had had a cholecystectomy performed.

Evacuation of the gall bladder in 12 females with pernicious anemia showed greater delay than in a group

of normal females (71.5 per cent evacuation during the first 40 minutes as compared with 84 per cent evacuation). Possibly the high excretion of fecal urobilinogen in pernicious anemia produces obstruction of the cystic duct with the result that the gall bladder wall suffers damage.—M. H. F. Friedman.

ULCER

JORDAN, SARA M.: *Peptic ulcer in the world of today.* (*J. Omaha Mid-West Clin. Soc.*, v. 5, p. 63, Aug., 1944).

The author states that peptic ulcer is largely the result of stress and strain in the individual and social life and therefore she believes that the incidence of ulcer will fall off greatly in post-war years. However, in the post-war years we shall have to contend with ulcer cases that first come to medical attention during the war years. The author believes that therapy should be in proportion to the severity of the disease. Therapy is based mainly on reducing both spasm and hyperacidity. Rest, neutralization of acid, anti spasmotics, change in mental attitude of the patient are all recommended as useful, even necessary. A regimen for both the bed-confined patient and for the ambulatory patient is presented. Perforation, hemorrhage and obstruction are the most common complications of ulcer. Perforation is handled solely as an emergency and should receive surgical attention at the earliest possible moment. The Meulengracht diet is not advocated in the treatment of hemorrhage. Rest, morphine, transfusions, and no food for at least two or three days are recommended. Obstruction is treated with reference to changes in body chemistry. The type of obstruction should be determined and surgery or medical therapy should be carried out as indicated. Gastric resection should be performed only as a last resort.—F. X. Chockley.

GARBAT, A. L.: *Diet regimen in peptic ulcer.* (*New York State J. Med.*, v. 44, p. 2015, 1944).

Uncomplicated peptic ulcer is a medical rather than surgical problem and each patient not under constant strict observation should be placed on a special diet. The dietary regimen should begin with simple foods and should gradually proceed to include more complex types of foods until a general diet is reached. The author's diet begins with hourly feedings of milk alone for 2 to 3 days, then includes eggs and custards, and eventually includes fish, chicken, lamb chops and light desserts. Raw fruits and vegetables are not used but fruit juices are given for the vitamin C requirements. Milk is taken freely but coffee is forbidden at all times. Weak tea and cocoa are allowed.

In addition to dietary management other measures must be taken. These include administration of antacids and spasmolytics, elimination of emotional disturbances and anxiety, adequate rest and avoidance of physical exhaustion, eradication of infections and foci of infection, and avoidance of tobacco and all alcoholic beverages.—N. M. Small.

ABRAHAMS, A.: *Smoking and duodenal ulcer.* (*Brit. Med. J.*, No. 4380, p. 798, Dec. 16, 1944).

The author expresses himself as being doubtful that a strong case has been made out implicating smoking in the etiology of duodenal ulceration. In the first place some of the worst cases of peptic ulcer have never been smokers, or had long ago given up smoking. Secondly, in the last 25 years smoking has been very common among women and yet the incidence of ulcers among women has not increased.—F. E. St. George.

SCURUMPF, A.: *Azotemia after gastric hemorrhage.* (*Acta med. Scand.*, v. 116, p. 191, 1943).

In 55 cases of gastric hemorrhage azotemia occurred in 43 cases. The blood urea was increased. In both bleeding and non-bleeding ulcers there was found a negative nitrogen balance. During the period of treatment of the bleeding ulcer by most common procedures the metabolism was characteristic of that of hunger. Initially the azotemia is due to undernutrition at the time when a nitrogen deficit is established. The rise in blood urea is only in part due to the absorption of blood from the intestine during gastric hemorrhage. No significance is attached to the anemia which is produced by the hemorrhage and the degree of anemia is not related to the azotemia. Total serum base and serum chloride and total base balance were found unrelated to the initial azotemia. In no case could the azotemia be attributed to a reduction in renal function.—D. A. Wocker.

THERAPEUTICS

MACKENZIE, D. H.: *An investigation into the use of sulphasuxidine in operations on the rectum and colon.* (*Brit. Med. J.*, No. 4378, p. 722, Dec. 2, 1944).

Thirty patients were examined. Eight cases received sulphasuxidine, eight received sulphaguanidine and the remaining fourteen received sulphathiazole. Colony counts of fecal cultures were made and films examined both wet and by Gram's stain. Gram negative organisms of the intestine were profoundly decreased by the sulphasuxidine. No effect was exercised on the growth of enterococci. No toxic symptoms or complications were observed.—F. E. St. George.

RICKETTS, H. T.: *Carbohydrate in the treatment of disease.* (*J. Am. Dietetic Assoc.*, v. 20, p. 365, 1944).

In diets of 2000 to 2500 calories per day, 80 to 100 grams of protein and 250 to 400 grams of carbohydrate are considered average. One school of treatment for diabetes aims at a diet sufficiently low in carbohydrate to prevent glycosuria; the other minimizes the ill effects of glycosuria and aims only to prevent ketosis. The control of diabetes by diet and insulin is described. Hypoglycemia, diseases of the liver, hyperthyroidism, sprue and other conditions are discussed, together with their dietary management with reference to carbohydrates.—Courtesy Biological Abstracts.

GARDINER, R. H.: *Intraperitoneal chemotherapy.* (*Brit. J. Surg.*, v. 32, p. 49, 1944).

The author advocates intraperitoneal chemotherapy be used in all emergency operations on the abdomen. He has found that sulfapyridine powder, suspended in sterile saline, produces excellent results when administered into the peritoneal cavity. Cases of apparently hopeless peritonitis due to acute appendicitis yielded remarkably well to treatment. This discharge was either reduced altogether or else its purulent nature was abolished. Directions for making the suspension are given. As much as 25 grams of sulfapyridine was inserted without evidence of toxicity. Intraperitoneal administration has several advantages over oral or parenteral administration. There is no apparent interference with the processes of healing.—F. E. St. George.

STEIGMANN, F., AND POPPER, H.: *The medical management of jaundice.* (*Illinois Med. J.*, v. 86, p. 164, Sept., 1944).

Bile salts are useful whenever it is desirable to produce a choleric action. The need for cholerisis may be due to any one of a large number of reasons. Chronic hepatitis and incomplete obstruction of the biliary tree are believed to be indications. In such instances it is preferable to induce the flow of a thin watery bile rather than a thick bile rich in organic materials. Unconjugated oxidized bile salts are best for this purpose. The recommended oral dose is 0.3 to 0.6 grams after meals. In addition to the choleric action they exert, the bile salts are additionally useful in aiding the absorption of fats and fat-soluble vitamins from the intestine.—G. N. N. Smith.

SMITH, E. A.: *Biliary constipation.* (*Clin. Med.*, v. 51, p. 151, June, 1944).

Water has an important role in determining the bulk of the stool. The water of the colon is determined to a large extent by the bile flow into the intestine. This is due mainly to the osmotic effect of the bile. Dehydrated stools are frequently encountered where the bile flow is not adequate. This "biliary constipation" is believed by some authors to be a common, if often unrecognized, occurrence. Therapy consists of administering either whole bile or the bile salts. The dosage is a matter to be adjusted to each patient's needs. The bile or bile salts soon induce bile flow and the stools rapidly become bulkier but softer and the patient does not experience distress on stool passage but experiences a greater sense of well-being.—D. A. Wocker.

SURGERY

COUNSELLOR, U. S., WAUGH, J. M., AND CLAGETT, O. T.: *Report of surgery of the stomach and duodenum for 1943.* (*Proceed. Staff Meet Mayo Clinic.*, v. 19, p. 586, Dec. 13, 1944).

By means of graphs and tables the authors present the trends in surgical management of gastric and duodenal disease. Of the total number of patients with duodenal ulcer, 38 per cent were treated surgically in 1928 but only 13 per cent in 1943. The authors attribute this to a definite change in the type of ulcer that comes to

surgical treatment: these are mainly perforating, bleeding, obstructing or intractable ulcers. Partial gastrectomy was performed with the same frequency as gastroenterostomy. Pyloroplasty is no longer performed.

Surgery for gastric ulcer occurred in 60 per cent of the total number of patients with gastric ulcer. This high figure is no doubt due to the necessity of determining by direct inspection whether a malignancy is present. Clinical history and roentgenographic examination frequently fail in this respect.

Partial gastrectomy was performed in 164 out of 323 patients subjected to surgery for malignant lesions of the stomach; total gastrectomy in 17, palliative procedures in 25 while the remainder (117 cases) were exploratory operations. The importance of periodic examination of the stomach is stressed: resection was performed on only 35 per cent of the cases diagnosed as malignant gastric lesions.

The mortality rates were: partial gastrectomy for duodenal ulcer, 0.5 per cent; for gastric ulcer, 1.5 per cent; and for malignancy of stomach, 4.9 per cent. Thorough preoperative preparation of the patient and extensive use of sulfa drugs are largely responsible for this low death rate.—R. L. Burdick.

MATHENY, D.: *Modern trends in gastric surgery through 1943.* (*Western J. Surg. Obstet. Gynec.*, v. 52, p. 475, Nov., 1944).

The author attempts to indicate the trends of gastroduodenal surgery. Gastric resection gives good results in gastric ulcer, the mortality due to gastric resection being less than 1 per cent. There is a 10 per cent error in roentgen diagnosis of gastric ulcer. Therefore radical surgery had less risk than medical prescription. Gastric resection is not the final answer to duodenal ulcer. Although it gives better results than gastro-enterostomy, Holmes and McSwain feel that one-half to two-thirds resection of the stomach is sufficient, after weighing risk against adequate lowering of acid. Failure to remove duodenal ulcer and pylorus is inadequate surgery. High postoperative acids require continued post-operative protection.

Hemorrhage cases should be operated on if over 45 and treated medically if under 45 years of age. Perforation requires simple closure routinely. Drainage is not required routinely. Evaluation of the time intervals from perforation to operation is not given. Once perforated, an ulcer will likely give continued trouble.

The author discusses an orthodox procedure as, 1) replacing patches of stomach with jejunal patches. 2) cholecysto-gastrostomy. Cancer of the stomach is discussed from the standpoint of pathology. Techniques of gastrectomy are discussed, including total and trans-thoracic resections. The usual stress of the modern surgeon is to lay upon pre- and post-operative management.—Wm. L. Snape.

HUTCHISON, W. B.: *Review of recent advances in large and small bowel surgery.* (*West. J. Surg. Obstet. Gynec.*, v. 52, p. 481, Nov., 1944).

Abbott and Miller showed the value of total de-

termination and of amino acids in wound healing. Gerwig and Stone presented a case of bowel polyposis with intussusception. Gibbs and Sutton reported 92 cases of intussusception in infancy and childhood. Diagnosis and treatment are reviewed in the conventional manner. Regional ileitis does not require radical therapy initially. The acute condition is seldom diagnosed pre-operatively and radiography is not important in acute cases.

The causes of death in high intestinal obstruction are not entirely settled. High obstruction death may be caused by dehydration, hypochloremia, achlorosis and uremia. Lower obstruction deaths are caused by prolonged distension and by gangrene of bowel wall. Treatment of obstruction should follow these rules: 1) restore electrolyte balance, 2) relieve distension by intubation of small bowel and removal of the obstruction, 3) do resection of bowel if necessary. Organic obstruction in which vascularity is not embarrassed may be treated as follows: 1) immediate postoperative obstruction is managed best by intubation, 2) late post-operative obstruction is managed best by relieving distension first by intubation and then by operation. Operative management for chronic ulcerative colitis seems to be still applicable in only a few selected cases.

A gangrenous and strangulated bowel may be present without radiographic evidence of obstruction. Polyposis of the large gut was studied in eleven cases under 14 years of age; bleeding was an outstanding sign. Nine of the cases studied were adenocarcinoma grade 1, two were adenoma. Treatment of Hirschsprung's disease should first be medical and surgical only if there is failure in the medical attempt.

Carcinoma of the right and left bowel is considered along with carcinoma of the rectum in a discussion of various operative procedures. Carcinoma of the anus is regarded as highly malignant regardless of the treatment. The fatal outcome may be lessened by more extensive operative measures. Pruritus ani may be treated by excision of perineal skin together with a flap coverage from the buttock.—Wm. S. Snape.

EXPERIMENTAL MEDICINE SECRETION

REHM, WARREN S.: *The effect of histamine and HCl on gastric secretion and potential.* (*Amer. J. Physiol.*, v. 141, p. 537-548, 1944).

A method is described for the measurement of the gastric potential and the rate of secretion of hydrogen ions from the same portion of the stomach. It was found that the potential of the non-secreting stomach, when saline was in contact with the mucosa, was between 70 and 95 millivolts. Histamine stimulation was followed by a decrease in the magnitude of the potential. The potential after reaching a new level remained relatively constant while the secretory rate continued to increase. In an attempt to determine the effect of the diffusion potential between the gastric secretion and the saline on the gastric potential, HCl solutions of a pH range of that of the gastric secretion were placed in contact with the mucosa and the effect on the

potential was determined. The increase in potential following this procedure was always less than the magnitude of the original decrease after saline. Application of HCl solutions of the above pH range to the resting stomach was followed by a decrease of the potential. After the HCl was replaced by saline, the potential of the resting stomach gradually increased to approximately its original level. Histamine stimulation, while the potential was still depressed, was followed by secretion and comparatively little change in the magnitude of the potential. With a phosphate buffer in contact with the mucosa histamine stimulation was followed by a typical decrease in the potential. The role of these factors in the decrease of the potential after histamine stimulation is discussed. Application of HCl solutions to the secreting stomach and subsequent replacement with saline resulted in some experiments in a marked decrease in the potential. This decrease in the potential was associated with a decrease in the secretory rate. On the basis of the results obtained in these experiments an attempt has been made to reconcile the conflicting reports in the literature on the relationship between gastric secretion and potential.—Courtesy Biological Abstracts.

MOTILITY

DREISBACH, R. H., VAN WINKLE, W., AND HANZLIK, P. J.: *Antispasmodic actions of "hypotensive" extracts on smooth muscles.* (*Arch. Internal Med.*, v. 74, p. 424, Dec., 1944).

Extracts of pancreatic tissue, free from insulin, histamine and choline have been claimed to give good clinical results because of their antispasmodic action on smooth muscle. The authors doubt the accuracy of these reports and do not believe the observations were carried out with sufficient attention paid to controls. They studied the effects of two extracts, one deproteinized pancreas, and the other padutin, obtained from urine or pancreas. Both extracts cause a fall in blood pressure when given intravenously to rabbits. When tested on longitudinal muscle strips from dog and rabbit intestine, depression of intestinal activity was obtained with very large doses of padutin but the same effect was obtained when the preservative alone, glycerine, was used. The other drug, depropanex, was found to be ineffective.—M. H. F. Friedman.

HELM, J. D., AND INGELFINGER, F. J.: *The effect of spinal anesthesia on the motility of the small intestine.* (*Surg. Gynec. Obstet.*, v. 79, p. 553, Nov., 1944).

Ten patients who were subjected to eleven abdominal operations for various indications were studied. Records of the motor activities of the small intestine were taken before the patients were operated. This was done by means of rubber balloons in the intestine. Records were also taken continuously throughout the course of anesthesia and operation. It was found that morphine and scopolamine premedication inhibited intestinal

motility. Spinal anesthesia had little or no effects on intestinal activity. This may have been due to the pre-medication. Therefore if the patient has received drugs like atropine, scopolamine, or morphine there will probably be no effect from spinal anesthesia and this treatment would not be efficacious in paralytic ileus as has been recommended.—Wm. J. Snape.

EXCRETION

ANNEGERS, J. H., SNAPP, F. E., PASKIND, L., IVY, A. C., AND ATKINSON, A. J.: *Retention of atabrine in animal body: excretion in bile and urine and effect on cholic acid output.* (*War Med.*, v. 4, p. 176, 1943).

White rats received subcutaneously daily doses of 5 mg. atabrine for 5 days. On the sixth day the body still retained 29.5 per cent of the drug. In dogs receiving the drug by mouth for a period of one week the liver was found to contain 6 per cent of the total drug twenty four hours after the last dose. Muscle and spleen retained only one per cent of the drug. The excretion of the drug in the bile was 9 per cent of the oral dose if the drained bile was readministered to the dog but only 4.8 per cent if the bile was not returned. The amount excreted in the urine was between 4 and 5.2 per cent. No atabrine was found in the feces following oral administration. The output of cholic acid was not diminished although in some dogs there was a temporary decrease.—F. X. Chockley.

STAINER, M., AND STAPLETON, T.: *Absorption and excretion of sulfonamides in children.* (*Lancet*, v. 1, p. 366, 1944).

Sulfathiazole, sulfaguanidine and succinyl-sulfathiazole were administered to a group of children every four hours in doses of 0.05 milligrams per kilogram body weight. After 48 hours of taking the drug the proportion of each drug excreted during the following five days were: sulfathiazole, 25.8 per cent, sulfaguanidine, 27 per cent and succinylsulfathiazole, 1.85 per cent. The slower the drug was excreted in the urine the higher was the concentration of that drug in the blood.—F. E. St. George.

PATHOLOGY

HAVENS W. P., WARD, R., DRILL, V. A., AND PAUL, J. R.: *Experimental production of hepatitis by feeding icterogenic materials.* (*Proceed. Soc. Exp. Biol. Med.*, v. 57, p. 206, Nov., 1944).

The mode of transmission of infectious hepatitis was studied on 19 individuals in two institutions. The infectious materials studied were derived from British and American soldiers and consisted of sera, stools and dehydrated filtrates of stool and urine extracts. After incubation periods of 56 to 70 days (average 64) three out of five subjects receiving icterogenic serum intracutaneously developed infectious hepatitis. Feeding icterogenic serum or feces to 9 other human subjects resulted in development of the disease in five subjects in 20 to 84 days (average 37).—H. Stilyung.

Acute Hepatitis. Clinical Observations in 63 Cases

By

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IT has been known for a long time that certain infections and selected toxic substances may cause liver damage. Ottenberg and Spiegel (1) have recently classified the multiplicity of causative agents. In a group of 63 cases admitted to the Metropolitan Hospital, the most common aetiological factors encountered in order of their frequency were infections, chemotherapy and systemic disease.

Infections. The infectious group comprised 38 patients, 15 of which were children. Contrary to the prevailing opinion that acute infectious hepatitis is a disease of young people, the age distribution of our series shows that 18 out of 23 cases were between the ages of 20 and 50, 2 cases between 50 and 60, 2 cases between 60 and 70, and 1 case between 70 and 80. Bloomfield (2) has found that two-thirds of his cases were also between the ages of 31 and 50.

It is important to remember that acute hepatitis may affect an elderly group of patients and may simulate extra hepatic obstruction. When the obstructive phase dominates the clinical picture, the differentiation from a mechanical obstruction may be difficult and the possibility of a hepatitis with intra-hepatic obstruction must be kept in mind.

While the exact etiological agent of infectious hepatitis is still unknown, experimental data suggest that a virus or several viruses are the possible causes. It is also generally accepted that acute hepatitis whether epidemic or sporadic is infectious in nature.

The chemotherapy group. The occurrence of hepatitis following the use of the sulfonamide group of drugs has been pointed out by many investigators, Watson and Spink (3), Long, Bliss and Finestone (4). In our series, 11 cases were seen. Sulfonamide was used in 4 of the cases for G.C. urethritis, sulfathiazole in one case for an alveolar abscess. In the remaining 6 cases, sulfadiazine was administered for intercurrent infections in the course of chronic liver disease. The amount of the drug used varied between 8 to 10 grams, icterus appeared 5 to 7 days following the intake of the drug.

The mechanism of jaundice following the intake of the sulfonamide group is believed to be due either to direct action of the drug upon the liver cells with subsequent degeneration, hemolysis, or to a combination of both factors. There was no evidence of hemolysis

in any of our 11 cases. The clinical picture was that of acute hepatitis as judged by the appearance of jaundice and our composite group of liver function tests. The advisability of the use of the sulfonamide drugs for inter-current infections in the course of chronic liver disease is rather debatable. Paterson, Deutsch, and Finland, (5) have found that the presence of liver disease is no contraindication to the administration of the sulfa drugs, unless there is evidence of severe portal cirrhosis, when greater caution should be exercised. Our experience differs somewhat from that of the above-mentioned authors. Six patients with known portal cirrhosis were admitted to the hospital for treatment of acute infections. Four of these patients were examined in the O.P.D. three to eight weeks prior to admission. All four patients were compensated, and liver function tests were within normal range. The exact status of the remaining two was not known prior to their admission. Sulfadiazine was given to all six in amounts varying from 9 to 12 grams. All patients developed intense jaundice, and liver function tests showed extensive hepatic impairment. One patient had marked nitrogen retention, oliguria, depression of cholesterol ester fraction in the blood and died in hepatic insufficiency five days after the administration of the drug. Two patients became markedly decompensated, developed ascites and one was still decompensated 4 months after admission. One patient developed marked hemorrhagic diathesis with a very low prothrombin level. The remaining two made a complete recovery, but the cephaline flocculation test remained positive for 6 months. One must state that the mere nature of a cirrhotic process with its remissions and exacerbations limits the evaluation of the relationship between the drug and liver damage. An episode of acute hepatitis in cirrhotics can be part and parcel of the disease precipitated by an acute infection. However, the hepatotoxic action of the sulfonamides cannot be ignored, and their use is not without danger in chronic liver disease.

Arsphenamines. In 9 cases acute hepatitis followed the use of arsphenamines. In 3 it occurred following the first few intravenous injections, in 1 hepatitis appeared after massive metapharsen therapy. In the remaining 5 cases, jaundice occurred at intervals ranging from 3 to 18 months after the use of arsenicals. There is still no unanimous opinion as to the exact mechanism of hepatitis following antiluetic treatment. Roholm, Krarup (6) and Bergstrand (7) are of the opinion that it is a form of epidemic hepatitis brought on by arsphenamines which lowers the resistance of the liver parenchyma. Other investigators, Sanes and Jordon (8) incriminate the drug itself which produces dif-

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fuse zonal and focal degenerative changes. Hanger and Guttman (9) have shown on biopsies from operative cases that it is primarily a cholangitis and pericholangitis with bile thrombi in the small biliary radicles without any damage to the liver cells. The observations of Hanger and Guttman were based on a group of cases of post-arsphenamine jaundice with clinical and laboratory data pointing to mechanical obstruction. Three of our own cases presented a similar clinical picture; the intra-hepatic obstructive phase was the dominating feature, and the cephaline precipitation was persistently negative in 2 cases and became positive in 1 case, two weeks after the appearance of jaundice.

Systemic. In 5 cases of systemic disease, hepatitis occurred at one time or another. Two were associated with lobar-pneumonia, and 3 with secondary lues. Pneumococcal infections are not uncommonly associated with sub-clinical jaundice. The icterus is thought to be due to one of several factors. Injury to liver parenchyma as a result of anoxemia, Rich (10), hemostasis with subsequent disintegration of R.B.C., Ham and Castile (11), bacteremia and bile solubility of the pneumococcus, Bachr and Klemperer (12). One cannot exclude however, the hepato-toxic effect of the chemotherapy which had been used in both cases. In both cases, liver function tests were indicative of parenchymal impairment and became normal three weeks after the disappearance of the jaundice.

Syphilis. Hepatitis in secondary lues is rather uncommon. It has been estimated that its frequency varies from .37% to 1.4%. All of our cases had generalized lymphadenopathy, macular skin eruptions, and one had a primary lesion of the labia majora. The serology was positive in two cases and negative in the third. Clinically hepatitis of secondary lues cannot be differentiated from epidemic hepatitis. Jaundice usually disappears with antiluetic therapy as it happened in two of our cases. The subsequent course of the third could not be followed. Warthin (13) believed that hepatitis is due to spirochetemia and found spirochetes in large numbers in the liver of a syphilitic patient. Others on the other hand disagree with his view since they have failed to demonstrate the organism in liver sections. Lichtman (14) is of the opinion that hepatitis in early lues is related to the specific infection itself and is a manifestation of the general toxemia of the disease.

Clinical picture. The clinical picture of acute hepatitis, regardless of the etiology presents a fairly distinct pattern. There are however, variations in the mode of onset, course and prognosis.

In children whose age in our group varied from 18 months to 15 years, the initial symptoms in 12 of the 15 were G.I. in nature. Generalized abdominal pains, anorexia, vomiting and diarrhea were the dominant prodromal symptoms. In 3 cases the disease was initiated with symptoms referable to the upper respiratory tract. The prodromata lasted from 3 to 5 days. Temperature was present in some cases. Jaundice appeared 3 to 5 days following the onset of prodromata and lasted from 7 to 26 days. In 1 case the

icterus persisted for 4 weeks and in another for 4 months. In the majority of the cases parenchymal damage became apparent 2 to 3 days after the onset of jaundice. In 2 cases, a phase of intra-hepatic obstruction dominated the clinical picture, and the possibility of a mechanical obstruction was entertained. All children except one left the hospital free of symptoms and laboratory tests showed no evidence of hepatic impairment at the time of their discharge. In one case however, laboratory data indicative of liver damage were present 18 months after discharge from the hospital. It would seem, therefore, that acute hepatitis, in children runs usually a benign course.

In the adult group the prodromal symptoms were either gastro-intestinal, upper respiratory or arthralgic in nature. In a number of cases there were no prodromata at all. Nineteen cases were admitted with anorexia, abdominal pains which were either generalized or localized to the right upper quadrant, constipation, nausea and vomiting. Eleven had no initial symptoms, patients becoming aware of dark urine, hypo or acholic stools. In five, gripppe, pharyngitis and sinusitis were responsible for their admission to the hospital. In 3, arthritic pains preceded the onset of jaundice. Fever was not a prominent symptom, being present in some cases and absent in others. Hepatomegaly was present in twenty-nine and splenomegaly in nine cases. Icterus varied in intensity and duration, and ranged from five days to twelve weeks.

Diagnosis. Diagnosis was arrived at on the basis of the clinical picture as stated above and laboratory data. The laboratory tests used were icteric index, Van den Bergh, cephalin cholesterol flocculation, cholesterol partition, albumin-globulin ratio, phosphatase, prothrombin level, duodenal contents, urine and stool examinations. The clinical picture plus this group of tests frequently repeated, will give sufficient information indicative of parenchymal impairment. There remain however, a group of cases in which the differentiation between extra and intra-hepatic obstruction cannot be made even with full utilization of clinical and laboratory data. In 9 cases, 3 of which belonged to the early post-arsphenamine group, there was such subjective and objective evidence of mechanical obstruction that surgery had to be resorted to in four cases.

Intra-hepatic obstruction. The mechanism of intra-hepatic obstruction has been explained in a number of ways. Eppinger (15) demonstrated that it results from the disruption of the continuity of the liver cells caused by necrosis of liver parenchyma and leading to bile stasis and bile thrombi. Althausen (16) is of the opinion that intra-hepatic obstruction is due to pressure upon the small bile radicles by regenerated hepatic parenchyma, which takes place in the recovery phase. A third view, as previously mentioned, is held by Hanger and Guttman who state that intra-hepatic obstruction is primarily due to a cholangitis, pericholangitis, and bile thrombi. The difficulties encountered in differentiating between intra and extra-hepatic obstruction are demonstrated by the following three cases:

Case No. 1—White female, age 32, was admitted to the hospital on 2/6/41 for excruciating right upper quadrant pain radiating to the shoulder and jaundice. Past history revealed abdominal pains of similar nature, one year duration, with recurrent attacks of jaundice which would subside within seven days. The essential findings were tenderness in upper right quadrant, liver two fingers below costal margin, jaundice and temperature of 101. Laboratory data were icteric index 57, Van den Bergh, direct positive, total cholesterol 200, cholesterol ester 106, urine positive for bile, negative for urobilinogen, stools acholic. A tentative diagnosis of stone in the common duct was made, and patient was operated on. No stones or other mechanical factors responsible for the jaundice were found. There were fibrinous patches over the liver and histological examination of biopsy showed necrosis of liver cells and engorgement of biliary radicles. After a somewhat stormy post-operative course, with temperature of 104, lasting for a number of days, patient made a full recovery.

Case No. 2—White female, age 24, was admitted 11/20/42 for a third attack of jaundice. The first episode occurred in November 1937, following anti-typhoid injection, and lasted from 6 to 7 months. The second attack occurred in November 1940, which lasted five months. The third attack was not associated with any fever, pain or anorexia. Essential findings were: liver—four fingers below costal margin, icteric index 75, Van den Bergh—direct delayed, cephalin flocculation—negative, total, cholesterol—449, cholesterol ester—257, duodenal drainage—negative for bile, urine—positive for bile and negative for urobilinogen and stools—acholic. Repeated laboratory tests were so persistently suggestive of a mechanical obstruction, that patient was subjected to a laparotomy. No evidence of mechanical obstruction was found.

Case No. 3—White female, age 60, admitted to the hospital on 8/4/41 with upper right quadrant pain, fever ranging from 101 to 102, weakness, vomiting, jaundice and a loss of 40 pounds within one year. A similar attack occurred six months prior to admission, consisting of pain in upper right quadrant, jaundice and fever. A cholecystectomy was performed eight years ago. Essential findings were tenderness r.u.q, liver—two fingers below costal margin, icteric index 53, Van den Bergh, immediate direct, total cholesterol 135, cholesterol ester—35, cephalin flocculation—3 plus, a.g. ratio—1/1, prothrombin level—53, stools—acholic, urine—positive for bile. The laboratory data were suggestive of parenchymal damage, but because of history of previous cholecystectomy, the age of the patient and marked loss of weight, the patient was subjected to surgical intervention. Laparotomy disclosed no mechanical obstruction, and histological examination of liver biopsy showed necrosis of liver cells and engorgement of bile radicles. All 3 cases made a full recovery.

Discussion. In analyzing our group of cases we were impressed with the variations of the clinical course. In the group of children, as previously stated, the disease ran a benign course. In one case, however, icterus

lasted for four months, and evidence of hepatic impairment was present eighteen months after discharge from the hospital. There were no fatalities in this group, although deaths have been reported in the literature.

A somewhat different course was observed in the age group between twenty and thirty, of which we had 24 cases. Nineteen left the hospital free of any clinical and laboratory evidence of liver damage. Of the remaining five, three had recurrences prior to hospitalization, and showed evidence of parenchymal impairment up to 19 months after admission. In 2 cases, icterus lasted 9 weeks and 12 weeks respectively, and parenchymal impairment was present 23 months after discharge. The age group of thirty to sixty years consisted of 21 patients. Two were recurrent cases, with evidence of liver damage 14 months after their discharge, two died in hepatic coma, one became compensated and continued to be so eight months after discharge; the remainder left the hospital apparently devoid of liver damage.

In the oldest group, of which there were 3 cases between the ages of sixty and eighty, there were no fatalities, despite the fact that two were subjected to surgery. Two left the hospital free of any indication of liver damage. In one, parenchymal impairment was evident eight months after discharge.

In charting the clinical behavior and prognosis of acute hepatitis, four types are met with, as pointed out by Bloomfield (16).

(1) Acute hepatitis with fatal outcome, as it occurred in two of our cases, who died from liver insufficiency.

(2) Recurrent attacks of acute hepatitis, as seen in five of our cases, where there is a potential possibility of progression to chronic liver disease. This relationship is further substantiated by the findings of Ratnoff and Patek (18). In 6½% of their series of Laennec's cirrhosis, there was a history of earlier episodes of jaundice.

(3) Acute hepatitis with apparent complete recovery as shown by persistent absence of parenchymal impairment from a clinical and laboratory point of view, of 21 cases which were followed up, 9 belong to this group, but it cannot be definitely ascertained at this time whether or not several or even all of them belong in this category since the follow up period of some 23 months is not an adequate period of time to allow for final conclusions.

(4) Acute hepatitis with apparent recovery, but with objective evidence of liver damage as shown in nine of our cases.

Summary. (1) A group of 63 cases of acute hepatitis was analyzed.

(2) The age incidence varied from 18 months to 80 years.

(3) Sulfanilamide drugs should be used with great caution in the presence of chronic liver disease.

(4) The clinical course of hepatitis is benign in children and varies in adults.

(5) Intra-hepatic obstruction often simulates extra-hepatic mechanical jaundice, and surgery may have to be resorted to for differential diagnosis.

REFERENCES

1. Reuben Ottenberg and Rose Spiegel. The present status of non-obstructive jaundice due to infectious and chemical agents. Medicine Vo. 22, number 1, February 1943, pages 27 - 71.
2. Bloomfield, A. L., Surgery 9, 61, 1941.
3. Watson, C. J. and Spink, W. W. Effects of sulfanilamide and sulfapyridine, Arch. Int. Med. 1940, 88, 825.
4. Long, P. H., Bliss, E., and Finestone, W. H. Toxicity of sulfanilamide, J.A.M.A., 1939, 112, 115.
5. Peterson, Osler L., Deutseh, Emanuel and Finland, Maxwell. Therapy with sulfonamide compounds for patients with damage to the liver. Arch. Int. Med. 72, 594, Nov. 1943.
6. Roholne K. and Krarup, N. B. Dichisto—Pathologic der Leber bei sogenannten slavassan, ikterus mittels aspirations biopsie intersicht. Arch. fur Dermatologie und Syphilologie 181, 521, 1940.
7. Bergstrand, H. Ueber die akute und chromische gelbe Leberatrophie neit besonderer heruck — sichtigung ihres epidemischen auftrittens in schweden, m. jahre 1927, Leipzig, Georg Thieme 1930.
8. Sanes, S. L., Jordan, J. W., Archives Dermat & Syphilology 32, 750, 1935.
9. Hanger, F. M. and Guttman, A. U., J.A.M.A., 115, 263, 1940.
10. Rich, C. A. Jaundice complicating pneumonia, Lancet, 1937, 1, 1046.
11. Ham, C. H. and Castile, W. R.. Relation of increased hypotonic fragility and erythro stasis to the mechanism of hemolysis in certain animals. Tr. A. Am. Phys. 1940, 55, 127.
12. Baehr, G. and Klempner, P., Degenerative and diffuse inflammatory diseases of the liver Internat. Cl. 1929, 2, 107.
13. Warthin, A. G. International Clinics, 21, 1, 189, 1911
14. Liehtman, S. S. Diseases of the liver, gall bladder and bile ducts. Lea and Febiger, hilad. 1942, page 712.
15. Eppinger H. Leberkrankheiten, Wien, Julius Springer 1937.
16. Althausen, T. I. Archives Int. Medicine 48, 667, 1931.
17. Bloomfield, A. L. Am. J. Medical Science, 195, 429, 444, 1938.
18. Ratnoff, O. D. and Patek, A. J. The natural history of Laennec's cirrhosis of the liver. Med. Vol. 21, number 3, Sept. 1942.

Drugs in the Treatment of Peptic Ulcer and Hypersecretion

By

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IN the treatment of peptic ulcer, drugs usually affect only the symptoms. These are caused chiefly by increased secretion of gastric juice. The reason is that in the ulcer cavity gastric juice causes an increased production of histamine-like substance. This substance stimulates secretion and finally leads to hypertrophic gastritis and to a vicious circle.

Among the consequences are: Secretion in the empty stomach, protracted and continued secretion after digestion of food, or overflow of the gastric juice into the esophagus, leading to soreness, pain and heartburn. Such discomfort is caused not by hydrochloric acid, but by pepsin. Drug therapy in the treatment of peptic ulcer is in reality not the fight against HCl, but against the invisible enemy, pepsin. The following test shows the action of pepsin, clearly:

Gastric juice is poured into one glass, and into another is poured gastric juice in which the pepsin has been previously destroyed by boiling. Thumb and index finger are rubbed together in both glasses. After a time a corrosive action can be felt on the skin of the fingers in the glass containing the unchanged pepsin.

As pepsin is rendered ineffective by neutralization, absorption, buffering or by evacuation of the gastric juice, the pain vanishes. In addition to the discomfort, there are characteristic severer and periodic pains. They are the result of increased inflammation at the margin and the base of the ulcer, and are caused furthermore by pyloric spasm.

Sodium Bicarbonate

is one of the oldest drugs. At the present time it is not in fashion. One objection to this drug is that it excites renewed secretion. However it only occurs when given in exorbitant doses, otherwise it reduces secretion.¹ This stimulation may be a "protective secretion" analogous to the abundant secretion of alkaline pancreatic juice which follows the intake of hydrochloric acid solutions. Pawlow, who first observed this reaction, believed hydrochloric acid to be the normal stimulant for pancreatic secretion. However, we demonstrated this pancreatic reaction to be only a "protective secretion" against hydrochloric acid.²

More important is that sodium bicarbonate, taken as a dry powder or in solutions higher concentrated than 1-2% (that is about a level teaspoon in 200 cc of water), may somewhat irritate the inflamed mucosa of the stomach with an active ulcer.

Another objection is the fear of alkalosis. The symptoms of alkalosis were first observed in France, several decades ago, and called "cachexie alcaline". At that time patients were given thirty to forty grams daily. In this country alkalosis seems to occur more frequently after the Sippy treatment.

However, the intake of sodium bicarbonate, or baking soda, with foods and otherwise, is customary, nevertheless, alkalosis has never been observed. The therapeutic dose is about 2-3 level teaspoons a day. This quantity does not cause alkalosis, even if taken regularly. The effect in the stomach is the immediate neutralization of HCl, with subsequent inactivation of pepsin. The resulting CO₂ relaxes the pylorus and

¹R. Ehrenmann, Internat. Beitrage Pathol. and Ther. Ernährungsstörungen Vol. 3, 1913.

²R. Ehrenmann and R. Lederer, Berl. Klin. W. No. 20, 1909.

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cardia. A rapid emptying of the stomach follows. CO₂ also has an analgetic effect. No larger distension results; therefore, no danger of ulcer perforation exists. If carbonated water is taken, such perforation may occur, as observed by the author. Taken on an empty stomach, sodium bicarbonate dissolves mucus and has a favorable effect on gastritis. There is, however, one drawback: It has no lining effect.

Sodium bicarbonate is unexcelled, when it is a question of emptying the stomach. It promptly relieves pain occurring several hours after meals or in the middle of the night. If milk is given instead, the stomach will remain full, and secretion continues. A patient, overcome by sudden severe pain while without soda or food at hand, can use "his own soda". By enforcing vomiting movements, he can accelerate the secretion of pancreatic juice into the stomach, and pain will cease.

Alkaline Earths

as Magnesium Oxide, Magnesium Carbonate USP, and Calcium Carbonate, have practically the same qualities as sodium bicarbonate, in regard to neutralization gastric secretion and pepsin. Besides, they have a lining and soothing action. Calcium carbonate has the stronger lining effect. It furthermore exercises an antiinflammatory action. Magnesium oxide, in turn, adsorbs large quantities of gas. One gram is able to adsorb 1000 cc of CO₂. Therefore, it gives no relief if taken on a full stomach.

Bismuth Subcarbonate

has no effect on HCl and none on pepsin. But it has a marked lining effect. Roentgenological examination proves that it settles in the ulcer cavity, protecting it against gastric juice and food, and preventing formation of the histamin-like substance. It absorbs wound secretion and dries the wound.

Aluminum Hydroxide and Aluminum Silicate

resemble bismuth in their action. However, if in a colloidal state, they are able to adsorb pepsin and hydrochloric acid. This is a purely physical procedure. No chemical conversion occurs.

The author observed these facts several decades ago, and subsequently introduced the drugs to therapy.³ Today they are widely used. Some uncertainty, however, exists as to their action. Our opinion is that such action depends on two processes after ingestion: Peptization, that is solution in HCl, and gelatinization of the colloidal Al. The colloidal Al is then able to adsorb hydrochloric acid, though only in relatively small quantities. More important, however, is its adsorption of pepsin. This occurs only in an acid or a neutral gastric content. Through the adsorption of pepsin, pain is eliminated. In a gelatinous state, the Al drugs have the same soothing effect as mucilaginous substances, i.e. colloidal solutions of cornstarch, barley gruel, gelatine and pectin. All these colloids, organic or metallic, have the same soothing effect on the mucus membranes, which fats and oils have on the skin. They furthermore, have a constipating effect in common.,

In addition, they exert a corrosive action. Silver-nitrate, formerly so popular, but now little used, may well have had a similar corrosive action. Because of these corrosive qualities, colloidal Al is used by factories for dyeing of materials.

After-effects are caused by the combination of Al with phosphorus in the intestines, which leads to a depletion of phosphorus in the bone structure. Rickets have been produced by feeding aluminum salts experimentally. It is generally believed that Al itself is not resorbed. The urine shows no increase beyond the normal trace. Nevertheless there is a certain degree of resorption with deposition in the liver. Both Al and bismuth are alien substances in the body. Used in cases of skin lesions, toxic effects have occasionally been observed. Al as well as bismuth therefore should not be taken continuously by the patients.

Colloidal Magnesium Silicates

are mostly hard and sandy. They adsorb pepsin readily, whereas their adsorption of hydrochloric acid is below that of aluminum drugs. They are not superior in any way.⁴

Belladonna and Atropin

are effective only if taken one-half to one hour before meals. If given after secretion has started, their action is greatly decreased or entirely lacking. It has been observed that a slight increase precedes the cessation of secretion.⁵ This, however, is of no clinical importance.

Belladonna drugs have an anti-spasmodic and analgetic effect. They delay motility and evacuation. Given together with alkalines, these remain longer in the stomach, prolonging the effect on neutralization and pepsin. Unless a slight dryness of the mouth is felt, there will be no effect on the gastric glands. Moreover, these drugs have the widest safety-margin of any of the alkaloids used in therapy. Even the effect of toxic doses can be controlled quickly by pilocarpin.

Gastric Mucin, Histidin

and other drugs widely advertised today have no real advantages.

A word on the method of administration may be added: Hard tablets may be harmful to the mucosa. Tablets should be soft and easily crushable. Powders should not be sandy, and should be taken, like crushable tablets, in the form of a suspension in water. Sodium bicarbonate, dry or in a concentrated solution, irritates the mucosa. Drugs should be taken either before or after meals, in accordance with their intended effect.

The following table demonstrates that it makes a great difference whether the drugs are administered by weight or by volume. In practice, the neutralization by volume is decisive.

⁴Brenhaus and Egerly, *An. Intern. Med.*, 14, 1941.
⁵Schiffman and Komarov, *Am. J. Dig. D.*, 8, 1941.

⁵R. Ehrmann, *Intern. Beitra. z. Path. U. Ther. d. Ernährungsstörungen*, Vol. 3, 1913.

Table

Neutralization
or absorption
of 1/10 N.HCl

Arrest of
Pepsin

Dose	Substance			
<i>Gram</i>				
1	Magnesium Oxide, Light	500 cc	+	Instantly
1	Magnesium Carbonate USP	300 cc	+	Instantly
1	Calcium Carbonate	200 cc	+	Instantly
1	Sodium Bicarbonate	125 cc	+	Instantly
1	Aluminum Hydroxide Colloidale	50 cc	+	About 15 Minutes
1	Aluminum Hydroxide	0 cc		None
1	Bismuth Subcarbonate	0 cc		None

*Level**Teaspoon*

1	Calcium Carbonate	600 cc	+	Instantly
1	Sodium Bicarbonate	550 cc	+	Instantly
1	Magnesium Carbonate USP	300 cc	+	Instantly
1	Magnesium Oxide, Light	250 cc	+	Instantly
1	Aluminum Hydroxide Colloidale	50 cc	+	About 15 Minutes
1	Aluminum Hydroxide	0 cc		None
1	Bismuth Subcarbonate	0 cc		None

Generally Magnesium oxide is considered the most effective neutralizing agent. It is correct that 1 gram of Magnesium Oxide neutralizes more HCl than any other substance. But, to neutralize 500 cc of 1/10 N. HCl, we need 2 level teaspoons. In contrast to that fact, less than 1 teaspoon of sodium bicarbonate is needed for the same quantity of acid.

SUMMARY

The different drugs have different indications.

Belladonna and Atropin check the secretion of gastric juice considerably, if given before secretion begins, and if administered in proportionate quantities. They help overcome pyloric spasm, and are analgetic. Taken

on a full stomach they delay the passage of food.

Alkalies and Alkaline Earths instantly neutralize HCl, reduce secretion and render pepsin ineffective. They have a different effect on the bowel movement. Magnesium and Calcium have a lining effect.

Sodium Bicarbonate has other specific actions. It empties the stomach quickly, by formation of CO₂. It has a beneficial effect on the accompanying gastritis. It is harmless if given in doses which are therapeutically sufficient. There can be no danger of alkalosis or subsequent secretion.

Bismuth Subcarbonate absorbs practically no hydrochloric acid, and no pepsin at all, but it is the best protective for the ulcer cavity. Because of its adhesiveness and oily consistency it is beneficial to ulcers and gastritis. It prevents the formation of histamine-like substances in the ulcer cavity.

Colloidal Aluminum Hydroxide and Aluminum Silicate render pepsin ineffective through adsorption. They are peptized and gelatinized in the gastric juice, and have a soothing effect similar to that of the colloidal starch solutions and mucilaginous substances. They have a corrosive quality which is perhaps the same as that of the formerly popular silver nitrate. They are not free from after-effects, and should not be taken by the patient on his own responsibility. The same is true for bismuth.

In contrast to aluminum and bismuth preparations, all the alkalies and alkaline earths are perfectly harmless, if taken in the required doses and concentrations. They are not alien substances in the organism. Considerably smaller doses are needed to absorb hydrochloric acid, and, what is more important, to render pepsin ineffective immediately.

Appetite and Obesity

By

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VARIOUS studies have shown that appetite tends to reflect body needs (1, 2, 3) but the excessive appetite associated with obesity would seem to be an exception to this rule. Another apparent exception is the decrease in appetite produced by undernutrition and fasting. This decrease was referred to in previous papers (3, 4, 5) and was attributed to dehydration. Similarly, the increased appetite associated with obesity appears to be explainable as a result of increased general hydration. In any case, this possibility and its bearing upon the problem of obesity seems to be worth considering.

The occurrence of water retention in cases of obesity has been pointed out by Newburgh (6) and an explanation of the tendency of adipose tissue to retain water as well as fat is suggested by the lymphatic-like

origin and structure of adipose tissue. Wassermann and his associates (7) found that adipose tissue develops from the same embryonic elements as lymph nodes and a lymphatic-like structure of adipose tissue is grossly discernible in fully developed human fat pads. I observed the lymphatic-like structure of adipose tissue in cadavers while serving as technician in gross anatomy at the College of Medicine of the University of Illinois (1916-1917). First, it was found that subcutaneous nodular cords, similar to lymphatic cords, could be palpated through the skin in the region of the brachial and femoral arteries of some of the fresh bodies that were brought to the morgue of the medical college. Incisions made to reach the arteries for embalming purposes revealed that the palpable subcutaneous lymphatic-like cords were adipose structures. Subcutaneous fat pads in regions like the gluteal region where nodular cords could not be palpated through

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the skin were therefore examined and found to consist of close formations of deep-lying lymphatic-like adipose cords which apparently could not be felt through the skin because of an over-lying closely knit (lymphatic terminal-like) adipose network. Like the subcutaneous lymphatics, the adipose cords showed frequent anastomoses and were found to converge in the lymph nodes of the axilla and groin. Similar relations between various internal fat deposits and lymph nodes were also found. The nodular structure of adipose cords reflects the location of valves in the lymphatics. The affinity of adipose tissue for fat is similar to that of the lacteals and the affinity of adipose tissue for water can be regarded as like that of the ordinary lymphatics. In short, adipose tissue gives the impression of being modified and fat-infiltrated lymphatic tissue and obesity seems to be appropriately referred to as "oily dropsy".

The water retained in adipose tissue evidently serves as part of the general reserve of body fluids and this, as indicated in the previous papers (3, 4, 5), normally determines the amount of appetite and digestive secretions and consequently also appetite and digestive capacity. Thus, the water in adipose tissue could account for an appetite sufficient to at least maintain the fat deposits but the initial over-development of adipose tissue seems to have a simpler explanation. That is, normal hydration, normal appetite and normal digestive capacity apparently include margins of safety which would seem to explain somewhat excessive food intakes when interest in fully satisfying appetite and the means to do this are present. My observations on rats indicate that all normal rats will eat enough to become fat if enough palatable and highly nutritious food is available. Uninhibited, normal human beings will apparently do likewise. Apart from this, appetite is likely to become excessive when hydration becomes abnormally increased, either because of the type of diet used or

the amount of food eaten or as a result of endocrine factors (as in menstrual edema and hydration associated with pregnancy) or after recovery from disease. Most commonly perhaps, the potentially obese individual is excessively hydrated at birth or becomes excessively hydrated soon after birth. The basis of an appetite sufficient to promote the development of obesity is thus assured and the subsequent obesity is likely to appear to have been inherited.

The foregoing helps to explain the occurrence of obesity but it does not suggest any possible simple remedy. Appetite can best be controlled by keeping hydration within normal bounds. A sufficient restriction of the food intake will, of course, reduce fat deposits but adipose tissue does not disappear when its fat content is reduced. Adipose tissue then simply tends to hold more water and the water may become a factor in increasing appetite. Nevertheless, the water content as well as the fat content of adipose tissue can be reduced by sufficiently prolonged, strict or specific food restriction but this can not be done without simultaneously depleting other reserves essential for the maintenance of normal body functions. It is known that reducing regimens can be carried to the point where indigestion and even anorexia develop. They are natural consequences of extreme dehydration. On the other hand, when the food intake is increased again after a period of restriction, reserves essential for normal functioning can not be fully restored without simultaneously restoring the fat and water content of adipose tissue. This at least has been my finding in many attempts, during over 35 years, to get rid of a small but undesired subcutaneous fat deposit and others seem to have similar experiences. In short, complete prevention of the excessive development of adipose tissue appears to be the best and perhaps the only satisfactory means of control.

REFERENCES

1. Davis, Clara M.: Amer. J. Dis. Child., 46:743, 1933.
2. Richter, C. P.: The Harvey Lectures Series XXXVIII, 1942-1943.
3. Hoelzel, F.: Amer. J. Dig. Dis., 11:71, 1944.
4. Hoelzel, F.: Amer. J. Dig. Dis., 10:121, 1943.
5. Hoelzel, F.: Gastroenterology, 1:970, 1943.
6. Newburgh, L. H.: Jour. Amer. Med. Assoc., 97:1659, 1931.
7. Wassermann, F.: Sitzungsber. d. Gesellsch. f. Morphol. u. Physiol. in Munchen, 42:43, 1933.

Disturbances in Sugar Metabolism After Subtotal Gastrectomy

By
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THE absorption of sugar in men and animals normally takes place in the small intestine, since the stomach is quite unable to absorb either water or glucose. The process of absorption by the small intestine is very complicated. Experimentally it has been found that the absorption of sugar follows certain laws which may be defined by the following two rules:

a) sugar is absorbed in a selective way.

b) the absorption of sugar does not follow the simple laws of diffusion.

Re a): The selective process in which the absorption of glucose takes place is evident in the experiments of Verzar and Laszt: out of a mixture of glucose plus sodium sulphate made isotonic with blood, glucose is absorbed five times as fast as the sodium sulphate solution. This holds good in the living animal; after death sodium sulphate is absorbed faster than glucose.

Re b): Cori, Magee and Reid, Groen, Ravden and Johnston, Carnot and Chassevant and others found that the stomach tries to dilute a sugar solution until an adequate but not isotonic optimal sugar solution results which is allowed to enter the duodenum. Cori stated that different sugars have a different rate of absorption in the intestine: glucose 100, galactose 110, levulose 43, mannose 19, xylose 15, arabinose 9. The absorption through the peritoneum, on the other hand, is equal for all sugars; it does not show any selection. Magee and Reid emphasize that 0.75 M glucose (13.5 per cent) is the optimal concentration for absorption. They show further that glucose is more readily absorbed than water. London and Kotschureff have given an explanation for this complicated process: because of the fact that the stomach cannot absorb sugar this organ produces an adequate concentration of sugar solutions for optimal absorption in the small intestine. We have to consider that a maximum of glucose absorption taking place in the intestine varies between 1.4 gms. per kg., an amount which cannot be surpassed (Timble and Maddock).

Baranyi and Sperber studied the absorption of glucose from very dilute solutions and found that it continued even after the concentration in the intestine had fallen below that of the blood. Groen stated that concentration and absorption time had a linear relationship to each other. Certain authors like Rayden and Johnston, Morrison and others could not confirm the findings of Cori, namely, that the amount of glucose absorbed had no relationship to the concentration. Varying concentrations run parallel to the absorption in volume and varying volumes run parallel to the absorption in concentration. When 200 cc. of 26.3 per cent glucose solution were introduced into the stomach, it was found that after one hour 9.8 per cent glucose remained in the stomach, 3.4 per cent in the duodenum and 2.6 per cent in the jejunum and ileum; when 200 cc. of a 50 per cent glucose solution were administered to the stomach, 5.3 per cent were found in the jejunum and ileum. Interesting findings were made by Groen, who claims that the absorption of a solution of glucose above 10 per cent is independent of concentration, i.e. the amount of glucose absorbed from concentrated solutions under standard conditions is a constant one.

In normal individuals the stomach has the function of watching the entrance of the duodenum. We have known for a long time that the pylorus is the organ of evacuation of the stomach. There are three components of evacuation: the gastric peristalsis, the gastric tone and the pylorus. The latter is much more potent than the other ones. When the stomach is empty the pylorus relaxes as in achlorhydria; this is not the case when hydrochloric acid is present in the empty stomach. Therefore the production of hydrochloric acid is the natural agent responsible for pyloric action. (Shay, Gershon and Cohen).

If the pylorus has been eliminated then a different situation is created. We can no longer control the volume and concentration of the solutions entering the small intestine. It is therefore interesting to study two types of abnormality and their relation to the sugar

absorption problem:

- a) gastric achylia where the pylorus reflex is damaged, and
- b) the condition after gastrectomy, where the pylorus is removed.

Re a): Shay, Gershon, Cohen, Fels studied the sugar absorption in cases of gastric achylia. They found a high incidence of abnormal blood sugar curves after administration of 100 grams of glucose; 48 per cent of cases of anacidity showed abnormally high curves and only 16 per cent of normal cases showed high blood sugar. It seems to me that the normal duodenal activity is based on the presence of free acid; experiments made previously show that an alimentary hyperglycemia can be controlled and prevented by the normal acidity of the stomach. Lack of acidity produces hyperglycemia.

Re b): The conditions after subtotal gastrectomy are different; two-thirds of the stomach have been removed, the pylorus does not exist any more, free acid is absent. The acid factor and the mechanical function of the pylorus are impaired and therefore the motility of the stomach is damaged in a high degree. If the stomach is the guardian of the selection of food, of the volume concentration and retention, this whole mechanism is now destroyed by the surgical intervention. Consequently, we find changes in the absorption of sugar through the intestinal wall.

Such experiments were performed by Johnston and Rayden in 1935 on dogs after Billroth I operation. They introduced solutions of glucose of varying concentrations into the stomach and let them remain there for an hour. After this time the abdomen was opened, the esophagus, stomach, duodenum, jejunum and ileum separately clamped off and their contents separately collected. The glucose concentration in the stomach was higher than in normal animals. In the small intestine the glucose concentration was below isotonic level. In men, after the same operation, the blood sugar curve was found higher than normal. I cite the figures published by Weddell and Gale:

Fasting	maximum rise	24 hours after
93	124	47
89	101	69
103	63	0

and the publication of Lamar, Largel, Delius Leroy: General anaesthesia has nothing to do with this manifestation; even under local anaesthesia hyperglycemia results.

The clinical significance of the removal of the stomach for the blood sugar curve has been studied by Lapp and Diebold, and Beckerman in 1932-33. The first mentioned authors found high values already half an hour after an intake of 100 grams of glucose and two hours later a rapid drop. They believe that the hypoglycemic reaction is characteristic for this type of course. Beckerman observed attacks in patients after gastrectomy. Such attacks consisted of weakness, dizziness, drowsiness, tremor, feeling of warmth and heat, sweating, uneasiness. He found such attacks in cases of gastrectomy, particularly after intake of bread, potatoes, milk, flour. In 30 cases he obtained very low

blood sugar figures and explained such attacks as hypoglycemic shock. In his deduction I find a certain contradiction when he claims that food rich in carbohydrates increases spontaneous hypoglycemia. Beckerman gives the explanation that hyperinsulinism may provoke the symptom of hypoglycemia after the administration of carbohydrates.

In 1936 Lawrence found rapid intestinal absorption in cases of gastro-enterostomy and duodenal ulcer. Symptoms like convulsions and nystagmus were observed in these patients; he explained these disorders on the basis of the incidence of oxy-hyperglycemia. Unusually rapid absorption of glucose from the intestine is the cause of these abnormal somatic reactions.

My own publication in 1939 in the Arch. Mal. App. Dig. had the title "Hyperglycemic Shock". A high blood sugar level has been described by Fiessinger and Biran and others after intravenous injection of glucose, especially, in cases of nephritis and hypertension, but never were signs of glycemic shock observed in normal individuals after the intake of great quantities of sugar. Even more than 1000 grams introduced by mouth showed only a slight elevation of blood sugar according to an observation by May.

As Delhouge, Koranyi and others had claimed, blood sugar curves after gastrectomy and gastro-enterostomy showed a special character. Normal patients revealed a blood sugar curve having a quick rise, a prolonged level and a slow decrease, whereas patients with gastro-enterostomy had a rapid rise and a slow fall ending in hypoglycemia.

My own experiments in patients after gastrectomy showed that the administration of 100 grams of glucose, in a 30 per cent solution, introduced directly into the jejunum caused a rapid hyperglycemia with characteristic clinical signs: nausea, vomiting, headache, cramps in the abdomen, coma, nystagmus. Even patients showing hypoglycemic figures in fasting condition revealed a very marked hyperglycemia after the administration of glucose. Different sugars worked in a different way. Glucose and sucrose provoked hyperglycemia, levulose was entirely indifferent. In cases of marked hyperglycemia the intake of sugar (glucose and sucrose) provoked attacks of nausea, vomiting, wide pupils, pain in the lumbar region and lowering of the blood pressure; these are signs of shock. These attacks developed 20 minutes after the administration of glucose or sucrose at the same time as the hyperglycemia set in. The fact that the levulose did not provoke such attacks could be easily explained by the slow absorption of levulose and the lack of hyperglycemia after the administration of this sugar. Similar attacks were never observed without hyperglycemia. I proposed in my first publication to name such shock "Hyperglycemic Shock". Another interesting observation was made; the attacks could be prevented by the administration of insulin, and patients suffering from these disorders after gastrectomy were advised to take small amounts of insulin (5-10 units) before meals; in this way attacks were completely avoided. My conception of hyperglycemic shock is very similar to that of Lawrence (England) who observed similar attacks

after gastro-enterostomy in 1936. He too attributed the attacks to hyperglycemia. In my opinion the stomach has a very marked regulatory function. By eliminating the pylorus this regulation fails, and too rapid absorption of sugar and hyperglycemia results. In this way many troubles following gastrectomy could be explained. Many cases of disorders after this operation were attributed to different causes as e.g. adhesions, anacidity, to the reduced volume of the stomach and even to jejunal ulcers. My observation reduced these suppositions to the simple formula of hyperglycemic shock.

In 1942 A. Schwartz, Rheingold and Necheles examined 15 cases of gastric operations regardless of their pathological manifestations; they could not find any connection between blood sugar level and such disturbances as I had described before and which they had observed likewise. They attributed the attacks to a rapid filling of the jejunum and reproached me for not considering the distention of the jejunum—due to the administration of glucose by direct introduction of sugar into the small intestine by a duodenal tube.

Two facts prove that the conception of the authors cannot hold good, namely:

1, that such disorders occur even if the glucose is administered by mouth (without tube) in the normal manner of intake, and

2, that levulose, administered by tube in the same concentration as glucose or sucrose, did *not* provoke any disorders at all, which would have taken place if the concentration, the rapid filling and the distention of the jejunum—as the authors suppose—were causing the attacks.

Besides these two arguments the publication of the authors discloses some weak points which should be mentioned.

An analysis of the 15 cases described by the authors reveals that one case is a gastro-enterostomy and not a gastrectomy (no. 15). Cases 7 and 12 have no decisive value being examined 12-13 days after the operation before the recovery of the operative changes could have been complete; case 9 shows gastric pain with no signs of shock; cases 3, 5, 6, 8, 10, 13, 14 show normal curves for blood sugar and no shock symptoms. Shock symptoms are present only in 4 cases, nos. 1, 2, 4, and 11.

Hyperglycemia was observed in case no. 1 (from 85-337); in case no. 2 (from 95-208); in case no. 4 (from 77-182); in case no. 11 (from 80-154).

The claim of the authors that in case no. 1 the nausea started while the blood sugar was still normal, is by no means astonishing. Experiments made by London and Kotschureff show that the tissues retain sugar; changing sugar levels could be attributed to the increased retention of sugar by the tissues (liver, spleen, muscles). It is likely that the rapid absorption of sugar leads to a filling of these organs before a definite level of blood sugar can be reached. Even after insulin injections such a retention of sugar has been observed.

Summarizing my opinion of the publication of Schwartz, Rheingold and Necheles I would emphasize: only 4 cases out of 15 show nausea and shock

Cases of Subtotal Resection.

Name	operated	fasting	100 grams'	glucose	Remarks
Age		blood sugar	30 min.	60 min.	
No.		pulse rate			
		blood pressure			
		eyeballs			
1) HB 4851/39	yes	70 p.r. 78 b.p. 110/75 eyeb's normal	155 p.r. 108 b.p. 100/65	160	dizzy 18 min. after glucose
2) MZ 63	yes	85 p.r. b.p. eyeb's normal	155	155	slight nausea 40 min. after glucose
3) CB 40 2147/34	yes 1934	80 p.r. b.p. eyeb's normal	160	160	slight headache
4) MF 25095/33	yes 1935	85 p.r. 72 b.p. eyeb's normal	280 p.r. 120 b.p. 160/25	135 p.r. 100 b.p. 150/25	nausea, dizzy soft balls 30 min. after glucose
5) GC 9246/36	yes 1938	70 p.r. b.p. 135/70 eyeb's normal	165 b.p. 100/60	105	vomit. nausea gas, 30 min. after glucose
6) J.Sch. 11497/36	yes 1937	60 p.r. 72 b.p. 150/100 eyeb's normal	120 p.r. 84 b.p. 180/100	100 p.r. 80	none
7) JK 48 16937/34	yes 10/19 1938	80 p.r. 72 b.p. 125/80 eyeb's normal	220 p.r. 120 b.p. 90/60	85 108 b.p. 120/70	dizzy headache, nausea, 20 min. after glucose
8) SB 8570/37	yes 1940	110 p.r. 72 b.p. 130/80 eyeb's normal	270 p.r. 106 b.p. 100/50	125 p.r. 80 b.p. 100/60	dizzy 35 min. after glucose
9) MG 50 620/37	yes	80 p.r. b.p. eyeb's normal	100 p.r. b.p.	100 p.r. b.p.	none
10) DdeT 8967/38	yes 11/4 1940	80 p.r. 64 b.p. 140/80 eyeb's normal	200 p.r. 100 b.p. 90/50	300 p.r. 106 b.p. 90/50	pain, vomit. soft eyeballs, dizziness, 25 min. after glucose
11) RJ 44	yes Dec. 1939	70 p.r. 68 b.p. 135/90 eyeb's normal	160 p.r. 96 b.p. 125/80	210 p.r. 106 b.p. 100/60	nausea 20 min. after glucose
12) AD 55 6600/33	yes 1922 1925	85 p.r. b.p. 150/80 eyeb's normal	125 p.r. b.p. 110/80	185 p.r. b.p. 110/70	dizziness, nausea, irregular pulse 30 min. after glucose
13) PHL 51 2230/36	yes 6/13 1940	75 p.r. 72 b.p. 140/70 eyeb's normal	160 p.r. 108 b.p. 105/60	110 b.p. 125/70	nausea, soft eyeballs, pupils dilated, 15 min. after glucose
14) NR. 3803/33	yes 11/8 1940	80 p.r. b.p. eyeb's normal	115 p.r. b.p.	50 p.r. b.p.	dizziness 15 min. after glucose

made daily recordings of her hours of sleep, water intake, appetite, food rejected, defecation, and general remarks as to her well being. The hemoglobin was determined by the Hellige Haemometer at the beginning and end of the experiment. Weight records were kept every week and the ascorbic acid of the plasma was determined every 3 to 4 days.

On the conclusion of the study the bisulfite binding substance (B. B. S.) of the urine was tested using the methods of Schrader (9). Six to seven days after the thiamin had been returned to the diet in 1.5 mg. amounts, the urine was again tested. In the case of

vitamin. The three other subjects were averaging from 76 to 80 per cent of this amount.

The ascorbic acid plasma level for the three days preceding eating the experimental diet was determined every day. This average pre-experimental ascorbic acid value maintained by 50 mg. of crystalline ascorbic acid plus any that might have been in the food, is to be used as the pre-experimental level against which to compare the subsequent plasma values.

The thiamin deficient diet immediately followed this preliminary period. When the ascorbic acid level of the plasma was determined three to four days after the

TABLE II
Showing Comparisons of Average Experimental Plasma Levels With the Pre-Experimental Level

Subject	A B		G H		H L		E P		
	Av. Levels	Plasma	% Difference	Av. Plasma	% Difference	Av. Plasma	% Difference	Av. Plasma	% Difference
Pre-Experimental	0.64			0.68		0.495		0.42	
4 wks Experimental	0.62		- 3.1	0.67		0.54	+ 9.0	0.56	+ 33.3
Last wk Experimental	0.64		0	0.63		0.62	+ 25.5	0.74	+ 76.3
Drop	0.56		-14.0	0.49		0.40	-23.7	0.40	- 4.7
After Initial Drop	0.65		- 1.5	0.66		0.61	+ 23.2	0.59	+ 30.4
Drop after removal riboflavin & niacin	0.52		-19.7						

one subject both urine and blood were tested. In this case beside the four weeks of a deficient thiamin diet the riboflavin and nicotinic acid had also been withdrawn for a period of ten days. For this subject a third test was made a little more than a month later when all the vitamin had been returned. The manner of collecting the blood and urine was followed as described by Friedmann and Haugen (10).

Results

In order that any question of the influence of the previous nutritional history might be eliminated in the interpretation of the experimental findings a dietary record of the food eaten was kept for eight days before the experimental diet was begun. When the nutritive value of the diet eaten for five days preceding the taking of 50 mgs. of crystalline ascorbic acid was estimated only the ascorbic acid from citrus fruits and tomatoes are considered. As Bessey and White (11) and Levowich and Bachelder (12) have pointed out the ascorbic acid value can be grossly over evaluated by including all sources of ascorbic acid when the method of cooking and the freshness of the food is not known. On this basis it was found that the average consumption of ascorbic acid for all subjects was satisfactory, averages ranged from 79 to 187 mg. per day, with the exception of one subject H. L. who failed to consume any citrus fruit or tomato for the last two days of the period making her average consumption 32 mg. The plasma level was not determined for this period except for one subject A. B. An average of seven tests made over a period of 20 days during which time a 25 mg. supplement of crystalline ascorbic acid was taken along with other foods. This record with the other results of the study are to be found in Table I. When the thiamin of the pre-experimental diet was estimated it was found that only one subject A. B. was meeting the recommendations of the Council for this

experimental diet was started, a drop in the values of all subjects was noted after which the levels rose. The average drop for this period was from 4.7 to 27.9 per cent below the average pre-experimental values. The levels were regained in at least 7 to 11 days by two of the subjects and in at least four days by the other two. A comparison of the average ascorbic acid values of the plasma with the pre-experimental level may be seen in Table II.

In the case of A. B. and G. H. the average level remained relatively constant whether considering the average for the four weeks, for the 17 to 24 days after the recovery from the initial drop or whether compared with the average levels for the last weeks of the experiment. In the case of the other two subjects these averages were all above the pre-experimental levels, ranging from approximately 9 to 76 per cent higher.

Though an effort was made to meet the energy needs of the subjects the weekly weighing showed that this was not accomplished in the case of H. L. and G. H. The hemoglobin of all subjects either remained constant or showed a slight rise during the experimental period. No subject reported a decrease in appetite or was any food ever rejected. A finding which is contrary to the reports of other investigators using a thiamin deficient diet. The subjects averaged 7 to 8 hours sleep a night. Despite this all reported fatigue increasing as the experiment progressed. Diarrhea, depression, palpitation, insomnia, headache, photophobia, frequent micturition, intolerance to sound, rough skin, thirst and nose bleed were all listed on the records kept by the subjects though fatigue was the only complaint found on all records. Nor did the complaint always persist throughout the experiment once it was noted. The subject who continued for ten days after removing riboflavin and nicotinic acid concentrates from the diet reported extreme fatigue. The necessity

of focusing the mind upon a problem required an effort almost physical in its magnitude.

The tests made on the urine for the bisulphite binding substance showed a drop of 26 to 43 per cent in the case of E. P. and G. H. respectively a week after a concentrate of 1.5 mg. of thiamin was given to these subjects. Both the blood and urine of A. B. were tested after she had been on the diet for 38 days and after the concentrates of riboflavin and nicotinic acid had been withheld for the last ten days. When these levels were compared with that of the blood and urine six days after the inclusion of a concentrate containing 1.5 mg. of thiamin, 2 mg. of riboflavin and 20 mg. of nicotinic acid and again a little more than a month later the results were surprising and contrary to what might have been anticipated. At the end of the 38 days the pyruvic acid (B. B. S.) value of the blood was 4.27 mg. per cent. A value which compares favorably with and is considered normal by Wortis et al (13) who used a method similar to the one used here. Six days later after all the missing vitamins had been returned the value had risen to 10.09 mg. per cent and more than a month later it was still 10.05 mg. per cent. The urine showed a similar increase with a rise of 18 per cent six days later and 42 days later the total rise was nearly 46 per cent. Since these results are so contrary to those reported where thiamin deficient diets have been used one might assume that with the added deficiencies of riboflavin and nicotinic acids the intermediary carbohydrate metabolism may have been more profoundly disturbed than occurs when thiamin alone is low. Titrating the dye with a solution of pure pyruvic acid the strength of which was approximately equal to the bisulphite binding power of the blood, gave values comparable to those of the blank test run with each ascorbic acid determination.

Discussion

Any discussion of the observations as set forth in this paper must be prefaced by the statement that further study is needed to determine the effect of a thiamin deficiency upon the ascorbic acid level of the plasma. From these experiments it seems to vary with the individual, since after four weeks of the deficiency two of the women showed no long range change in plasma levels and two, one after three weeks showed a significant increase. The transitory drop of the plasma value after thiamin had been removed from the diet which was shown by all subjects can not be regarded as a specific function of the thiamin since the same drop occurred when riboflavin and nicotinic acid were withdrawn. If one were so bold as to venture a possible explanation for the results observed in this experiment after so brief a study one might turn first to the scheme of consecutive steps of the intermediary metabolism of carbohydrates as set forth by Meyerhof (14) and then to the outline as suggested by Potter (15) in which he assigns the probable point of action of these vitamins in this complex system. Viewing these outlines from the comfort of an arm chair it would not seem too remote a possibility that if thiamin, riboflavin and niacin were withdrawn singly or together from the diet a strain might be exerted in this system

and that a great burden might be placed on ascorbic acid causing the vitamin to be withdrawn from the blood to be used by the tissues with a resulting drop in the plasma value. As the body achieved a readjustment in the balance, presumably from the stored vitamins, the ascorbic acid value of the plasma might rise. It is conceivable that the rise in the ascorbic acid values of the plasma as the diet progressed might be only apparent. The higher reducing value of the plasma might be due to the reducing action of some product of the disturbed carbohydrate metabolism. It has been suggested that pyruvic acid reduces the dye but this was not confirmed in this experiment. This hypothesis of increased reducing substances causing an apparent increase in the ascorbic acid level of the plasma may seem unnecessary for the increase in ascorbic acid of the plasma might just as well be due to the decreased requirement of ascorbic acid by the tissues as the carbohydrate metabolism is upset, with a resulting rise in the plasma value. Of course both these factors could be operating to produce the rise.

Why two subjects showed no rise in ascorbic acid values, might be explained by the degree of the disturbance in the carbohydrate metabolism. It is true that the subjects showing no average increase in ascorbic acid values were found to have been consuming the highest amount of thiamin before the experiment was undertaken and it will be noted that the bisulphite binding value of the blood plasma of A. B. was regarded as normal at the end of the experimental period, however, G. H. showed the highest bisulphite binding values for the urine though at the end of the 6 day ingestion of a thiamin concentrate she also showed the greatest reduction in the B. B. S. value of the urine. It is regrettable that no ascorbic acid determination accompanied these tests.

The sudden rise observed from time to time in the ascorbic acid of the plasma was studied in relation to a possible effect of menstruation upon the ascorbic acid levels. Nickelsen et al (16) reported that out of eight women studied four showed a sharp increase in the fasting level of plasma ascorbic acid during the middle of the menstrual cycle. In the women of this study the abrupt rise found in the recorded levels of G. H. occurred on the 15th day of the cycle, the rise for H. L. was found to be on the ninth day, for A. B. a rise occurred on the third and fourteenth days and for E. P. on the last and the third days of the cycle.

Summary

The effect of a thiamin deficient diet upon the ascorbic acid level of the blood plasma was studied in four women over a period of four weeks. The experimental diet as planned contained not more than 0.5 mg. of thiamin per 1000 calories of food eaten. The ascorbic acid values of the plasma were maintained by the ingestion of 50 mg. of crystalline ascorbic acid per day. The experimental plasma values which were compared with those of a pre-experimental level were also maintained by the same amount of crystalline ascorbic acid.

The removal of thiamin from the diet caused a temporary lowering of the ascorbic acid values of all subjects. The one subject tested showed a similar effect

when the riboflavin and niacin concentrates were withdrawn. Two of the subjects showed a significant rise

in the plasma level as the experiment progressed. No change was observed in the other two subjects.

REFERENCES

- Hopkins, F. G. and B. R. Stater: Effect of Incomplete Diets on the Concentration of Vitamin C in the Organs of Rats, *Biochem. J.* 29, 2803, 1935.
- Sure, B., R. M. Tieis, and R. T. Harrelson: Influence of Avitaminosis on Ascorbic Acid Content of Various Tissues and Endocrines, *J. Biol. Chem.* 129, 245, 1939.
- Dann, M.: Influence of Diet on Ascorbic Acid Requirement of Premature Infants, *J. Clin. Invest.* 21, 139, 1942.
- Dodds, M. L., and F. L. MacLeod: A Survey of the Ascorbic Acid Status of College Students, *J. Nutrition* 27, 315, 1944.
- Farmer, C. J. and A. F. Abt: Titration of Plasma Ascorbic Acid as a Test for Latent Avitaminosis C. Nutrition: The Newer Diagnostic Methods p. 114, 1938, Millbank Memorial Fund N. Y.
- Taylor, C. M.: Food Values in Shares and Weights, Macmillan Co.
- Langford, C. S. and H. C. Sherman: Nutrition 1941-1942, Annual Review of Biol. Chem. 12, 398, 1943.
- Todhunter, E. N., R. C. Robbins, and A. McIntosh: The Rate of Increase of Blood Plasma Ascorbic Acid after Ingestion of Ascorbic Acid. *J. Nutrition* 23, 309, 1942.
- Schrader, G. A.: Improved Method of Iodometric Determination of Pyruvic Acid, *J. of Lab. and Clin. Med.* 25, 250 1939-40.
- Friedmann, T. E. and G. E. Haugen, The Determination of Keto Acids in Blood and Urine, *J. Biol. Chem.* 147, 415, 1943.
- Bessey, O. A. and R. L. White: Ascorbic Acid Requirement of Children, *J. Nutrition* 23, 195, 1942.
- Levowich, T. and E. L. Bachelder, Ascorbic Acid Excretion at Known Levels of Intake as related to Capillary Resistance, Dietary Estimates and Human Requirements, *J. Nutrition* 23, 399, 1942.
- Wortis, H. E., Bueding and W. E. Wilson: Bisulphide Binding Substance (B. B. S.) in Blood and Cerebrospinal Fluid, *Soc. Exper. Biol. and Med. Pro.* 43, 279, 1940.
- Meyerhof, Otto: Oxidoreductions in Carbohydrate Breakdown: Biological Symposia V, 143, 1941.
- Potter, Van R.: The Role of Vitamins in Energy Transformation, *J. A. D. A.* 19, 488, 1943.
- Nickelsen, Olaf, A. L. Dippel, and R. L. Todd: Plasma Ascorbic Acid During Menstruation, *J. Clin. Endo.* 3, 600, 1943.

Effect of Concentration of Pepsin and the Differential Susceptibility of Jejunal Segments in Experimental Jejunal Ulcers in the Dog

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THE concentration of gastric pepsin is known to vary in both normal individuals (1, 2, 3, 4) and in those with disease (2, 3, 4), and it was of interest to us to determine if the concentration of pepsin influences peptic ulcer formation. Gunzberg (5) reported that the more concentrated the solution the shorter the period required for digestion. Schiffrian (6) used 3 per cent pepsin in HCl in producing peptic ulcers in rats while Driver et al. (7) used 2 per cent pepsin in HCl in their studies on dogs. That acid is an important factor in peptic digestion has been brought out by several investigators (8, 9, 10).

It was also desired to determine if there is a differential susceptibility to ulcer formation in different parts of the jejunum when various concentrations of pepsin are used.

METHOD AND TECHNIQUE

The jejunum of dogs under Dial-urethane* anesthesia was brought to the abdominal surface and three adjacent segments of about four inches each beginning about five inches from the ligament of Treitz were selected with due regard for an adequate blood supply

for each segment. These loops were cannulated and inserted into the abdomen. The solutions to be tested were made up about an hour before the start of each day's experiment. The solutions contained 0.1 per cent, 1.0 per cent or 2.0 per cent pepsin, in N/10 HCl, and were perfused through the loops at the rate of about 2 cc. per minute. After perfusing from 4 to 20 hours, the loops were removed, split along the mesenteric line and examined grossly and microscopically for peptic digestion.

An arbitrary means for recording the severity of the damage was adopted and is described as follows: (1) represents a condition in which there is a slight surface necrosis of the mucosa. (2) designates a deeper necrosis involving at least one-third of the thickness of the mucosa of the entire area with smaller areas (from $\frac{1}{2}$ cm.² to 2 cm.²) showing necrosis as deep as the submucosa. (3) indicates necrosis of practically all the mucosa with some patches extending into the circular muscle. (4) was applied to a loop having areas of necrosis extending to the serous coat or to a frank perforation.

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*The Dial-urethane was generously supplied by The Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

Each loop was scored according to this scheme and the average taken for each loop in each series. Beginning with the ligament of Treitz the loops were numbered I, II, and III from proximal to distal. Four series of experiments were run, the results of which are given in Table I.

TABLE I
Effects of Concentration of Pepsin and Position of Loop in Ulcer Formation

		severity				
Series A:	Loop I	0.1% pepsin*	in N/10 HCl			
15 dogs	Loop I	0.1%	"	"	"	1.40
	" II	1%	"	"	"	1.73
	" III	2%	"	"	"	2.15
Series B: 15 dogs	Loop I	2%	"	"	"	1.27
	" II	1%	"	"	"	2.07
	" III	1.1%	"	"	"	2.20
Series C: 10 dogs	Loop I	N/10 HCl				.40
	" II	"				.56
	" III	"				.50
Series D: 3 dogs	Loop I	0.9% NaCl				.00
	" II	"				.00
	" III	"				.00

From Table I it seems that pepsin at a concentration of 0.1 per cent is just as effective in producing ulcers as higher concentrations of the enzyme. The location in the gut seems to be more important than the concentration of the enzyme. Thus it is shown that the susceptibility of the jejunum to ulcers increases distally: loop No. III was almost two times as liable to necrotic lesions as loop No. I. This finding was confirmed by another series of experiments using a slightly different technique. Instead of three short loops a single segment of gut was taken reaching from the mid-portion of the duodenum to a point in the jejunum corresponding approximately to at least the distal end of loop No. III in series A, B, C, and D, Table I. In these experiments only one solution was used, 0.1 per cent pepsin in N/10 HCl. Out of 15 dogs 12 showed more damage to the mucosa in the

distal portion of the segment, two showed more damage in the proximal portion and one showed no damage at all.

Hydrochloric acid alone produces partial destruction of villi with an occasional deeper necrosis. (Table 1, series C.). This also was confirmed by using one long loop as described above. In seven dogs the damage with HCl alone was about one-third as much as when pepsin was present. Three of these seven showed no necrosis at all.

In controls using water the mucosa remained normal.

SUMMARY AND CONCLUSIONS

- Different levels of the jejunum of dogs were exposed to solutions of pepsin of varying concentrations (0.1, 1.0 or 2.0 per cent) in N/10 HCl.
- Control experiments were run with N/10 HCl, 0.9 per cent NaCl and water.
- The percentage of pepsin employed apparently was not a factor in the degree of digestion of the mucosa since there seemed to be about as much damage with one concentration as with others.
- The more distal loops of the gut used in these experiments seemed to be more susceptible to the action of pepsin in HCl than the more proximal segments.
- In order to confirm the above findings a series of 15 dogs was run as controls using a single loop covering at least the maximum portion of the gut employed in the first four series. The results in 12 of these dogs corresponded to the findings in Table 1. There was more damage in the proximal portion of the loop in two of the animals while one showed no damage. This same technique was employed on seven more dogs using N/10 HCl alone which produced about one-third as much damage as pepsin plus HCl.
- The high incidence of marginal ulcers following gastro-jejunostomy may possibly be reduced by making the anastomosis as near the ligament of Treitz as possible.

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REFERENCES

- Polland, W. S. and Bloomfield, A. L.: Quantitative Measurements of Pepsin in Gastric Juice before and after Histamine Stimulation. *J. Clin. Invest.*, 1929, 7:57.
- Polland, W. S. and Bloomfield, A. L.: The Diagnostic Value of Determinations of Pepsin in Gastric Juice. *J. Clin. Invest.*, 1931, 9:107.
- Helmer, O. M., Fouts, P. G. and Zerfas, L. G.: Gastro-intestinal Studies. I. Gastric Juice in Pernicious Anemia. *J. Clin. Invest.*, 1932, 11:129.
- Mullins, C. R. and Flood, C. A.: A Study of Gastric Pepsin in Various Diseases. *J. Clin. Invest.*, 1935, 14:793.
- Gunzberg, A.: Ueber eine Beziehung von peptischen Geschwüren zur Pepsinkonzentration. *Arch. f. Verdauungskr.*, Berl., 1924, 33:133.
- Schiffman, M. J.: Production of Experimental Jejunal Ulcer. *Proc. Soc. Exp. Biol. and Med.*, 1940, 45:592.
- Driver, R. L., Dozier, G. S. and Denham, H. C.: Effect of Various Chemical Agents Affecting Permeability of the Mucosa on the Formation of Ulcers. *Science*, 1943, 98:158.
- Exalto, J.: Ulcus Jejune nach Gastroenterostomie. *Mitteil. a.d. Grenzgeb. d. Med. u. Chir.*, 1911, 23:13.
- Mann, F. C. and Williamson, C. S.: The Experimental Production of Peptic Ulcer. *Ann. of Surg.*, 1923, 77:409.
- Mathews, W. B. and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer. *Surg., Gyn. and Obs.*, 1932, 55:265.

Effect of Hydrostatic Pressure on the Experimental Production of Ulcers

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IT has been demonstrated that intraintestinal pressure varies considerably in dogs and man. For example, Abbott et al. (1) reported for man a basal "tonus pressure" of 11 to 15 cm. H₂O, with peristaltic waves raising it to 20 or 30 cm. H₂O, and occasionally to 60 cm. H₂O. Sherrington (2) found a normal pressure of 2 to 4 cm. H₂O in the intestine of etherized dogs which was confirmed by Owings et al. (3) and Sperling et al. (4). The latter group found the intraintestinal pressure in man to be 20 cm. H₂O in simple obstruction and about 30 cm. H₂O in simple obstruction with peristalsis. Seventy-five cm. H₂O was found in closed obstruction (3). An unusual observation was made by Stone and Firor (5) on two patients whom they were treating for ulcerative colitis. In the course of the treatment, a temporary complete obstruction was made in the lower ileum affording an opportunity to measure intraintestinal pressure at a known time after the obstruction was produced. This measurement was made by thrusting into the intestine a hollow needle connected to a water manometer. In both cases five hours after the bowel had been closed the pressure exceeded 150 cm. H₂O.

In a previous paper (6) we reported the production of ulcers in the intestine of dogs by exposing a loop of the intestine to a solution of 0.1 per cent pepsin in N/10 HCl with just enough pressure to cause a flow of about 2 cc. per minute.

The high incidence of intestinal distention prompted us to determine whether hydrostatic pressure influences ulceration of the alimentary tract in dogs.

METHOD AND TECHNIQUE

Dogs were anesthetized with Dial-urethane,* the abdominal wall incised and a loop of the small intestines about 18 inches long was selected which reached from the mid-portion of the duodenum to approximately the junction of the upper third with the middle third of the jejunum. Both ends of the loop were cannulated so that solutions could be introduced into it and withdrawn at will. The loop was then replaced into the abdomen and exposed to a solution of 0.1 per cent pepsin in N/10 HCl under various hydrostatic pressures. The pepsin solution in the loop was drawn off hourly and fresh solution was added simultaneously without a marked change in the pressure. The loops were exposed for 360 to 720 minutes or until perforation occurred which could be noted by a rapid fall in the solution in the column. The loops were then re-

moved and examined for damage.

The pressures employed were 0, 45, 90 and 135 cm. H₂O, and the results are given in Table 1 along with control experiments using isotonic saline instead of the pepsin solution at pressures of either 90 or 135 cm. H₂O.

In all cases where 0.1 per cent pepsin in N/10 HCl was used there was some necrosis of the intestinal wall. At zero pressure the usual picture was a necrosis covering about one-third of the total area of the loop and extending in some instances to the serosa but in most cases only through about one-half of the mucosa. In all cases but two where hydrostatic pressure was used a perforation occurred and the damage was progressively worse as the pressure was increased. The time for perforation to occur became less as the pressure was increased as shown in Table 1. One dog at 45 cm. hydrostatic pressure with pepsin solution died at the end of 300 minutes with no perforation. One dog also died with no perforation at the end of 300 minutes in the 90 cm. hydrostatic pressure experiments with pepsin solution. The incision was made in the latter dog before he was in deep anesthesia, and the abdominal musculature was somewhat spastic rendering the intra-abdominal pressure considerably higher than usual, which in our opinion, accounted for the delay in perforation.

In controls exposing the gut to 90 or 135 cm. hydrostatic pressure with physiologic saline there was no perforation even though the exposure was for 120 to 720 minutes. These loops were atonic and stretched but showed no necrosis.

DISCUSSION

It is suggested that the pronounced effect of hydrostatic pressure on ulcer formation is due to three factors: 1. Mechanical stretching. The length and the diameter of the loop were increased by about one-third thereby causing a thinning and weakening of the intestinal wall. 2. Decreased blood supply. Landis (7) found the mesenteric capillary pressure in the rat to be 30 cm. H₂O and in the guinea pig 38.5 cm. Since it is quite likely that the capillary pressure in the intestine of dogs is of this order, it is evident that the pressure employed by us, either 90 or 135 cm. is sufficient to cause a marked retardation of blood flow even though the intestine may have some ability to recover its blood flow after its interruption by inflation of the loop (8, 9). 3. Increase in penetrability of pepsin. It has been reported that high hydrostatic pressure increases absorption in the intestine (10, 11), facilitating the absorption of substances not readily absorbed (10). By using various chemical agents which influence ab-

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*The Dial-urethane was generously supplied by the Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

sorption. Driver, et al. (12) were able to increase the incidence of ulcers over controls, and it is probable that in the experiments reported here, pepsin penetrated into the mucosa and deeper layers of the gut more readily under pressure.

In connection with these investigations the high incidence of ulcers among aviators is of considerable interest. In this group the neurogenic factor undoubtedly plays a major role in the etiology of ulcers, but it must be equally true that the intra-gastric and intra-intestinal distention to which aviators are subjected, particularly in rapid ascent after uncontrolled diet, con-

tributes to the severity of the damage to the alimentary tract wall.

SUMMARY

1. Loops of intestines of 48 dogs were exposed to 0.1 per cent pepsin in N/10 HCl under various hydrostatic pressures.

2. A rise in intraintestinal pressure resulted in a marked increase in the extent of peptic digestion which led to perforation in a short time. At 45 cm. pressure the average time for perforation was 300 minutes; at 90 cm. pressure, 82 minutes; and at 135 cm. pressure only 41 minutes.

TABLE I
Effect of Hydrostatic Pressure on Ulcer Formation

Solution	Hydrostatic Pressure	Number Dogs	Number Perforations	Time Exposed (minutes)	Average Range
0.1% pepsin* in N/10 HCl	0	15	0	685	360-720
"	45	10	9	300	65-565
"	90	11	10	82	60- 90
"	135	12	12	41	13- 70
0.9% NaCl	90	6	0	630	495-720
"	135	6	0	445	495-720

*Merck N. F. Powdered

REFERENCES

- Abbott, W. O., Hartline, H. K., Hervey, J. P., Ingelsinger, F. J., Rawson, A. J. and Zetzel, L.: A Method for the Measurement of Intraintestinal Pressure and its Clinical Significance. *Am. Jour. Med. Science.*, 1940, 199:879.
- Sherrington, C. S.: Postural Activity of Muscle and Nerve. *Brain*, 1915, 38:191.
- Owings, J. C., McIntosh, C. A., Stone, H. B. and Weinberg, J. A.: Intraintestinal Pressure in Obstruction. *Arch. Surg.*, 1928, 17:507.
- Spertling, L., Paine, J. R. and Wangensteen, O. H.: Intraluminal Pressure in Experimental and Clinical Intestinal Obstruction. *Proc. Soc. Exp. Biol. and Med.*, 1935, 32: 1504.
- Stone, H. B. and Eitor, W. M.: Absorption in Intestinal Obstruction; Intraintestinal Pressure as a Factor. *South. Surg. Trans.*, 1924, 37:173.
- Driver, R. L., Chappell, R. H. and Carmichael, E. B.: Effect of Concentration of Pepsin and the Differential Susceptibility of Jejunal Segments in Experimental Jejunal
- Ulcers in the Dog. *Amer. Jour. Dig. Dis.* 1945, 12:166.
- Landis, E. M.: The Capillary Blood Pressure in Mammalian Mesentery as Determined by the Micro-injection Method. *Am. Jour. Physiol.*, 1930, 93:353.
- Lawson, H. and Chunnley, J.: The Effect of Distention on Blood Flow Through the Intestine. *Am. Jour. Physiol.*, 1940, 131:368.
- Oppenheimer, M. J. and Mann, F. C.: Intestinal Capillary Circulation During Distention. *Proc. Staff Meet. Mayo Clin.*, 1942, 17:427.
- Dohyns, G. J. and Dragstedt, C. A.: Intraintestinal Pressure and Absorption from the Intestine. *Proc. Soc. Exp. Biol. and Med.*, 1933, 30:707.
- Elman, R. and Aird, I.: Observations on Intraintestinal Pressure with Special Reference to Absorption of Saline. *Proc. Soc. Exp. Biol. and Med.*, 1934, 32:1620.
- Driver, R. L., Dozier, G. S. and Denham, H. C.: Effect of Various Chemical Agents Affecting Permeability of the Mucosa on the Formation of Ulcers. *Science*, 1943, 98:158.

Increased Intra-Abdominal Pressure as a Means of Inhibiting Perforations Due to Pepsin Solutions Under Hydrostatic Pressure in the Small Intestines of Dogs

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IN previous papers we have shown that 0.1 per cent pepsin in N/10 HCl produced more necrosis in the

small intestine when hydrostatic pressure was applied than when the pressure was just sufficient to permit a flow of about 2 cc. of solution per minute (1, 2). Perforations occurred in an average of 41 minutes with

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135 cm. hydrostatic pressure and 82 minutes with 90 cm. hydrostatic pressure.

In the course of these experiments one dog was used whose anesthesia was not deep and in which the abdominal muscles were quite spastic. When this dog's abdomen was opened the intestines were forcibly expressed from the incision by the intra-abdominal pressure. After cannulation of the experimental loop considerable force was necessary to replace the viscera into the abdomen and to close the incision. Closure was made with clamps taking up about 2 cm. of the width of the abdominal wall on each side of the incision. After closure the abdominal muscles remained spastic throughout the duration of the experiment.

due to respiratory embarrassment caused by the 45 cm. pressure below the diaphragm.

DISCUSSION

An increase in intra-abdominal pressure inhibits perforation but seems not to inhibit the severity of the necrosis.

It is probable that the intra-abdominal pressure decreases the blood supply to the gut. Lawson and Chumley (3), experimenting with dogs' intestines, found that an intraintestinal pressure of less than 41 cm. H₂O caused a momentary interruption of blood flow through the loop. Between 41 cm. H₂O pressure and mean arterial pressure the blood flow was interrupted with partial recovery in a few seconds. This

TABLE I

Effect of Pressure in the Abdomen on the Time for the Appearance of Perforated Ulcers in the Gut

In the lumen of the intestine		In the abdomen		No. of Dogs	No. of Perforations	Time Exposed (minutes)	
Solution	Pressure	Solution	Pressure			av.	range
0.1% pepsin in N/10 HCl	90 cm. H ₂ O	0.9% NaCl	20 cm. H ₂ O	4	4	116	70 - 185
"	"	"	45 cm. H ₂ O	17*	12	178	75 - 480
"	"	Nothing	Atmospheric	11	10**	82	60 - 90

* Five of these dogs died before perforation occurred. See text.

** The dog that failed to perforate is the one which had the high intra-abdominal pressure.

Perforation did not occur in this dog with 90 cm. of intraintestinal pressure during the five hours that he lived. This seemed to us to indicate that the intra-abdominal pressure was considerably higher in this animal than in the other dogs of our series and the pressure outside the gut was thought to be the reason for the inhibition of perforation.

On the basis of this reasoning the following experiments were performed:

A group of dogs was treated as described in (1) except for the introduction into the abdominal cavity of a rubber tube extending through a stab in the abdominal wall to the outside and connected with an upright burette. The intra-abdominal portion of the tube was perforated at several points to insure free flowing of saline into the abdominal cavity. A towel was fastened around the abdomen as an abdominal binder and saline was introduced into the burette to any desired height, thus constituting a counter-pressure to the pepsin solution in the lumen of the intestine. The results of these experiments are given in Table 1.

When the pressure was 90 cm. in the intestine and the counter pressure was atmospheric, the time for perforation to occur was 82 minutes. At the same intraintestinal pressure and a counter pressure of 20 cm. of saline the time was increased to 116 minutes while a counter pressure of 45 cm. of saline increased the time to 178 minutes or 185 minutes if we use the times for perforation to occur in the 12 dogs that lived. In the five dogs that died the deaths were considered to be

recovery was prevented by encasing the loop in plaster of Paris, a procedure closely resembling our own.

The use of the abdominal binder decreases the expansion of the abdominal wall obviating the necessity for large quantities of saline in obtaining the desired intra-abdominal pressure.

It is possible that an abdominal binder may have clinical use in certain instances where it is feared that perforation may occur as in the critical period of patients with typhoid fever and in the case of high altitude fliers who are subjected to an increased intraintestinal pressure due to expansion of gas present in the gastrointestinal tract. It is unlikely that such a binder would seriously impair blood flow to the gut wall since this tissue has remarkable ability to recover its blood flow after its interruption by pressure in excess of that which a binder would produce (3, 4).

SUMMARY

1. The time for perforation to occur in dogs' intestines was studied by exposing the intestinal mucosa to a solution of 0.1 per cent pepsin in N/10 HCl under 90 cm. hydrostatic pressure and using intra-abdominal counter pressures of either 20 cm. or 45 cm. of saline.

2. The time for perforation to appear was lengthened by raising the intra-abdominal pressure, varying directly with the pressure. When the intra-abdominal pressure was atmospheric the time for perforation was 82 minutes; when the pressure in the abdomen was 20 cm. saline the time was increased to 116 minutes and at 45 cm. pressure, to 185 minutes.

REFERENCES

1. Driver, R. L., Chappell, R. H., and Carmichael, E. B.: Effect of Hydrostatic Pressure on the Experimental Production of Ulcers. *Am. J. Dig. Dis.* This issue.
2. Driver, R. L., Chappell, R. H., and Carmichael, E. B.: Effect of Concentration of Pepsin and the Differential Susceptibility of Jejunal Segments in Experimental Jejunal Ulcers in the Dog. *Am. Jour. Dig. Dis.* This issue.
3. Lawson, H. and Chumley, J.: The Effect of Distention on Blood Flow Through the Intestine. *Am. Jour. Physiol.*, 1940, 131:368.
4. Oppenheimer, M. J. and Mann, F. C.: Intestinal Capillary Circulation during Distention. *Proc. Mayo Clinic*, 1942, 17:427.

Pruritus Ani

By

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THE tribulation induced by pruritus ani may be almost insufferable. Even in the mildest cases it causes nervousness, irritability and sleeplessness in addition to the local discomfort. More serious forms of the disorder may present the physician with a symptom complex so distressing to the patient that he would gladly tear away the skin of the affected parts if he could obtain relief by so doing.

The sensation of itching is noted so frequently by normal individuals that it is considered physiological. Ordinarily slight friction such as scratching or rubbing causes the sensation to disappear. However, itching becomes pathological when the sensation is annoying or persistent. The mechanism of pruritus is not altogether clear but it is quite likely that it is a form of hyperesthesia. The latter may be produced by the elaboration of a histamine-like substance from endogenous sources as in urticaria, or in response to foreign material from without as in parasitic infections (1) or chemical irritants as in contact dermatitis. Kaposi explained many years ago how scratching could intensify itching but more recently Sulzberger and Wolfe (2) have suggested that a toxin capable of causing skin irritation may be present in the blood, and that after scratching more toxic material is brought to the involved area by means of the increased circulation, occasioned by the trauma. Whether or not this irritating toxin is histamine or the so-called "H" substance has not been proved.

Pruritus ani is a regional type of inflammatory skin reaction, the nature of which is exceedingly complex. The involvement may be minimal and periodic in which instances the simplest measures suffice to bring relief, but often the skin changes are so severe that only through the ingenuity of the physician and perseverance of the patient can the successful control of symptoms be brought about. There is no general agreement as to the etiology of the condition or the most effective therapy. The very number of theories as to the cause and cure are ample testimony as to their inadequacy, but some of the underlying factors have been discussed at length by Stokes (3). He groups the varied etiological constituents of pruritus ani into five divisions

and it is informative to consider them separately.

Physiological Mechanism:

The sweating apparatus of the anogenital area (apocrine glands) produces an excretion which has a higher pH than ordinary sweat (eccrine glands), contains protein, and excess carbohydrates. This type of secretion between two moist folds of skin furnishes an ideal culture medium for fungi and yeast organisms. The excess CHO normally found in the apocrine excretions may be further increased by a diet high in starches and sweets. Such foods, through the process of skin hydration, directly predispose to pyogenic and fungus infections, while alcoholic beverages exert a similar effect. It is further emphasized that a diet high in carbohydrates tends to encourage infection of intestinal contents thus promoting the growth of both fungus and pyogenic flora. The secretion of fat by the skin is a physiological defense mechanism but there is some reason to believe this function is minimal in pruritus ani. When sebaceous material is deficient the use of soap quickly removes the oily protective coat and leaves instead alkali which is not only irritating but probably causes a localized sensitivity to other substances such as metals (mercury, sulphur), drugs (salicylic acid, tars), allergens of a protein character, and presumably also to fungi, yeast and bacteria.

Infective Mechanism:

In the preceding paragraph it has been revealed how physiological conditions may profoundly affect the character of the bacterial flora in and about the anal opening. The most common infective agents in this area are the fungi and they may be demonstrated in many cases by direct scrapings or culture. Castellani stated that "Pruritus ani is, as a rule, a form of latent epidermophytosis without the usual symptoms of an ordinary epidermophytosis being present."

Terrell and Terrell (4) believe that ninety per cent of all cases of pruritus ani are due to fungus infection. They feel, as do others, (1-6) that local pathological conditions such as fissures, fistulas and hemorrhoids have been overstressed as a cause of anal pruritus. The author has seldom noted permanent cures following surgical procedures such as excision of fissures, repair of fistulas or removal of hemorrhoids.

Terrell and Terrell (4) maintain that the pruritus

ani and vulvae so often encountered in diabetes is usually due to local fungus infection rather than the systemic condition. However, other investigators claim that in diabetes there is a direct relationship between pruritus and hyperglycemia. (5) I am in accord with the latter opinion because some of the most extensive cases of pruritus ani I have ever encountered have been in patients with uncontrolled diabetes. They have uniformly improved with proper management of the diabetes, often without any local treatment whatever. This may be due to a reduction in CHO of the diet, as well as control of the glycosuria, but pruritus ani in diabetes may certainly be due to the systemic disturbance alone and demonstrations of fungi in the lesions by no means disproves this contention.

Sutton (6) also thinks that pruritus ani is more commonly due to monilia and trichophytosis than to any other cause, with aggravation of the local condition due to trauma and treatment. Excoriations often cause breaks in the skin which offer a portal of entry for all of the organisms normally found in this area such as streptococci, staphylococci, colon bacilli, fungi, monilia yeast cells and trichomonas (7). Contrary to common belief, gastro-intestinal parasites rarely cause pruritus ani (3). Pinworm infestation does cause temporary irritation about the anal opening especially in children, but the presence of this organism is easily detected by inspection and anoscopy examination and eradication of the oxyuriasis is accompanied by prompt relief from the local symptoms.

Psychogenic Mechanism:

Stokes maintains that there are always tension factors in the background of a chronic anal pruritic and the writer has noted many examples where the itching was a focal manifestation of a neurotically predisposed skin. "After fixation of the attention to the anal region, often by a local infective process, such as trichophytosis, the patient tends to set up a vicious circle of projection of his anxieties upon the perineum." (3)

Such a chain of events is difficult to interrupt unless the victim is thoroughly instructed as to how continued scratching may serve to set up irreversible skin changes.

Mechanical Factors:

Because of the anatomical arrangement of the anal area it is constantly exposed to trauma. Irritation is produced by the stool, especially if it is dry and hard or contains too much cellulose which may scrape the recto-anal mucosa. The ever-changing tension of the anal sphincters, rubbing of clothing, scratching, walking, enema tubes and, finally instrumentation, are all mechanical factors contributing to the development of pruritus ani. Many cases begin with an insignificant scratch or fissure.

Stillians (8) believes the use of dry toilet paper leaves a thin film of fecal matter on the anus and that this may be an important cause of itching in this region. Toxic material such as indole and skatole coming out of the rectum in the form of liquid or gas may be very irritating (9) and the perianal rawness and erythema noted after several loose stools lends support to the theory that some digestive juices may reach the

perineum without becoming altered chemically.

Allergic Mechanism:

Sensitization to specific foods, chemicals or drugs may be present at the beginning or develop during the course of the disease and in protracted cases this possibility should be explored. Phenolphthalein and a gum commonly used in laxatives and ice cream are common offenders among the ingested materials while resorcin, mercury, salicylic acid, and cocaine are often highly irritating when applied locally. In the author's experience sensitization to these chemicals is often expressly intensified by a preceding or concomitant fungus infection. The possibility of bacterial allergy must also be considered, but evidence for this has not been proved to the satisfaction of everyone.

Symptomatology:

As the name implies the most outstanding symptom of pruritus ani is intense itching and burning, which is characterized by remissions and exacerbations. Flare-ups often occur at night when the body is warm, thus interfering with rest and sleep. The condition may be acute or chronic. In the former there is redness, edema, excoriation, vesiculation, and sometimes weeping from demodex areas. In cases of longer standing there are usually lichenification, induration, and pigmentation, as these changes are indicative of chronicity. In the recalcitrant state the skin may be whitish in appearance, smooth and glistening, leathery, dotted with pigmented spots, or lie in deep folds radiating from the anal orifice.

Treatment:

There is no specific treatment for this symptom complex. All factors must be taken into account and therapy individualized for each patient. Careful history taking and persistence in a logical regimen will lead to relief if not cure in most instances. Measures for control of pruritus ani may be divided into three categories—systemic, local, and miscellaneous.

Systemic:

In chronic cases it is frequently noted that marked intensification of the disorder may accompany a period of nervous stress and when the tension is relaxed there is amelioration of the local pruritus. While this observation is no argument for formal psychotherapy in the average obstinate case it does suggest that an accurate appraisal of a patient's reaction to environment may be in order. Psychoneurosis is so manifest in some that suicidal tendencies may develop, in which case hospitalization is mandatory. (7)

Weight reduction can be helpful in the management of anal pruritics who are too fat. The author and others feel that obesity is a cause which is often overlooked.

The vulnerability of diabetics to monilia and fungus infections has already been discussed. It has also been mentioned that the pruritus ani and vulvae of diabetics has, in the writer's experience, frequently been cured by the control of the diabetes alone. Sutton (6) and Hesselteine (10) believe that diabetics are highly susceptible to mycotic organisms because dextrose favors their growth. Whatever the reason, maintenance of a

proper blood sugar level is a sine qua non in diabetics who have pruritus ani, and the local application of fungicides is of distinctly less importance.

Turell has observed a patient with localized pruritus ani in pellagra and effected a cure with the use of nicotinic acid. There is reason to believe that nicotinic acid and other members of the B-complex have much to do with skin metabolism and the physiology of the sebaceous glands. If nutrition is faulty, then B-complex may be an adjunct to treatment.

There is a menopausal type of pruritus vulvae and ani which usually responds readily to estrogenic hormones. One-half to one milligram of stilbestrol daily by mouth is adequate and it may also be given in suppositories. If there are objections to this form of treatment, 10,000 International units of estrone may be given intramuscularly at weekly or bi-weekly intervals.

Stokes (3) recommends a reduction in the carbohydrate content of the diet, and elimination of excess roughage. These measures are beneficial in most cases and the use of bran, nuts, whole wheat, raw fruits and vegetables is interdicted by the author. Stokes reduces or eliminates the consumption of alcoholic beverages and gives dilute hydrochloric acid by mouth. He states that allergic individuals with irritable bowel syndrome are benefited by calcium administration in addition to hydrochloric acid. Stools are examined for parasites (though, as previously noted, this is rarely important) and cultured. Occasionally it may be wise to change the intestinal flora. When specific food allergens are suspected, the elimination diets of Rowe may be employed because, as in other skin manifestations of allergy, intradermal or scratch tests seldom give accurate information. Milk, wheat, eggs and chocolate are common offenders. (11)

Local:

There is general agreement on the premise that local treatment suffers much more from the "sins of commission" rather than "omission." Most cases observed by internist and dermatologist alike have been grossly overtreated. (1-3-6)

Simple measures to insure scrupulous cleanliness are utmost in importance. Brunsting (1) stated that if local hygienic conditions were ideal, the functional element in pruritus ani would assume a place of major importance in the disease. Stokes (3) advises his patients to mop gently after each stool with a pledge of cotton soaked in 1:4,000 potassium permanganate. The use of dry toilet paper should be avoided. Many authorities do not like to use keratolytic and antipruritic drugs because patients are often sensitized to them. The author is particularly wary of salicylic acid, resorcin, sulfur, and ammoniated mercury. One per cent phenol in boric acid may be useful as a local application.

Mild astringents, keratolytics, antipruritics, and antisepsics have been recommended by Speare and Mabrey (9) who also emphasize the necessity of keeping the anal region clean by washing with soap and water after each bowel movement. The soap should be rinsed completely away with clear water. Many patients are relieved by these simple methods.

When the pruritus is acute, hot or cold boric acid compresses, sometimes alternating, give considerable relief. Sutton (6) recommends the removal of all grease and oil, and daily applies a 2 per cent aqueous solution of gentian violet. Sitz baths of 1:3,000 potassium permanganate may be beneficial at times. Castellani's carbolfuchsin paint has been found very useful by Stokes (3) who employs it diluted with water 1:3.

X-ray therapy enjoys a reputation for effectiveness which is hardly justified. In practice one notices that the better the constitutional factors are managed, the less frequently X-ray is needed. Roentgen therapy may relieve itching in many cases, although there are plenty of exceptions to this, but it does not cure the cause of the disease. Speare and Mabrey (9) were not impressed with the benefits of X-ray. Tomlinson (7) gives weekly X-ray treatments (75 r each) for eight doses, while Stokes (3) uses 400 r in six doses and if there is no improvement abandons this form of treatment.

In some series (8) local diseases such as fissures, hemorrhoids, cryptitis, proctitis, papillitis, etc., were present in forty per cent of the patients. Occasionally eradication of such lesions is followed by relief of pruritus but such instances are unusual. Recurrence following a brief remission is the rule. Some patients respond better if attention is given to complicating skin lesions such as fungus infections of the feet and seborrheic dermatitis. (7)

Miscellaneous:

A number of more or less radical procedures may be undertaken in case all other methods have failed. Ball (12) described a method for severing the superficial nerve filaments in the perianal region. Patients obtain relief following this procedure, but itching usually recurs in 3 to 6 months. Steinberg (13) has obtained satisfactory results with the perianal injection of Gabriel's solution (oil of sweet almonds, containing 0.5 per cent nupercaine, 1.0 per cent phenol and 10 per cent benzyl alcohol). Speare and Mabrey found that the solution used by Steinberg caused fibrosis and obtained relief in 70 per cent of patients by the subcutaneous injection of 3 to 5 cc. of alcohol. One quadrant at a time of the anal area is anesthetized by procaine, and then injected with the alcohol. Swinton (14) has had favorable responses with a similar method, but others (11) feel that the tendency to abscess formation and sloughing make the procedure undesirable.

Reich et al (15) obtained gratifying results in fifteen cases of intractable pruritus vulvae by injecting a warm solution (olive, almond and peanut oil containing 2 per cent procaine and 5 per cent benzyl alcohol) into the fatty tissue of the labia. A technique for surgical excision of the affected skin has been described by Scott and Young (16) but they emphasized that it should be employed only where all other methods have failed. Turell (17-18) had favorable experience in tattooing affected parts with mercury sulfide and Cantor (11) lauds tattooing with mercuric sulfide plus the operation of tattoo neurotomy as the procedure of choice. Stone in 1916 and later Wilson (19) described a technique of stippling the entire perineum with 95 per cent alco-

hol. A 26-gauge needle inserted perpendicularly is used and the procedure is carried out under general anesthesia. Two to four minims of absolute alcohol are injected under the skin at each point and the injections are about one-fourth inch apart. Care must be taken that the needle is through the derma and yet not too deeply into the subcutaneous fascia or abscess formation will result.

The author has employed this technique in many of the most obstinate cases with satisfactory results in most. It can be carried out in the office using intravenous anesthetics (evipal or pentothal sodium) but hospitalization for a day or two is the better way. Detailed case reports will not be given, but the experiences of one of my patients are worth mentioning. He had suffered with pruritus ani for fifteen years and when I first saw him he had just completed his third course of X-ray therapy. These had been fairly expensive and in his own words, "only made me worse."

The skin was the leathery texture characteristic of the intractable anal pruritic. The stippling technique resulted in complete relief for ten months, but at that time there was a slight recurrence. A repetition of the procedure resulted in apparent cure as the patient had no symptoms at the end of four years.

Conclusions:

1. Pruritus Ani is a symptom complex—not a disease.
2. A helpful outline of the varied etiological factors has been presented.
3. There is no cure, but when all phases of the disorder are taken into account most patients can be relieved.
4. Diabetes is a frequent cause and may be relieved by controlling the hyperglycemia.
5. Stippling the perineum with absolute alcohol may relieve many intractable cases.

REFERENCES

1. Brunsting, L. A.: The Treatment of Common Diseases of the Skin, *J. Lancet*, 60:438, 1940.
2. Sulzberger, M. B., and Wolf, J.: Pruritus and Its Treatment, *M. Clin. North America*, 19:971, 1935.
3. Stokes, J. H.: Pruritis Ani—Clinical Analysis, *New Internat. Clin.*, 1:147, 1940.
4. Terrell, Emmett H., and Terrell, Robert V.: Pruritis Ani, *South. M. J.*, 31:907, 1938.
5. Winkler, M.: Etiology and Pathogenesis of Pruritus. *Jadassohn's Handbuch der Haut- und Geschlechtskrankheiten*, Berlin. Julius Springer, Vol. 6, Sec. 1, page 343, 1927.
6. Sutton, R. L.: Gentian Violet as a Therapeutic Agent, *J.A.M.A.*, 110:1733, 1938.
7. Tomlinson, C. C.: The Etiology and Treatment of Some Types of Pruritus. *Jour. of Omaha-Midwest. Clin. Soc.*, 4:82, 1943.
8. Stillians, A. W.: Therapy of Pruritus, *J.A.M.A.*, 114:1627, 1940.
9. Speare, G. S., and Mabrey, R. E.: New England J. Med., 223:274, 1940.
10. Hesseltine, H. C.: Diabetic or Mycotic Vulvo-vaginitis, *J.A.M.A.*, 100:177, 1933.
11. Cantor, Alfred J.: Pruritus Ani, *American Journal Digest. Dis.*, 10:254-261.
12. Ball, C. B.: The Rectum: Its Diseases and Developmental Defects. London: H. Frowde and Hodder and Stoughton, page 332, 1908.
13. Steinberg, N.: Recent Advances in the Treatment of Rectal Diseases by Injection Methods in Ambulatory Patients, II—Pruritus Ani, *New England J. Med.*, 215:1019, 1936.
14. Swinton, Neil W.: The Injection of Alcohol in the Treatment of Pruritus Ani, *S. Clin. North America*, 19:689, 1939.
15. Reich, Walter J.: Button, Helen; Nechtow, Mitchell J.: A New Treatment for Intractable Pruritus Vulvae, *American Journal Obs. and Gyn.*, 45:1036-1038, 1943.
16. Young, Forrest; Scott, W. J. M.: Radical Operation for Intractable Pruritus Ani, *Surgery*, 13:911-915, 1943.
17. Turell, Robert: Tatooing (Puncture) with Mercury Sulfide and Other Chemicals for the Treatment of Pruritus Ani and Perinei, *J. Investigative Dermatology*, 3:289, 1940.
18. Turell, Robert; Buda, A. M., and Marino, A. W. M., Arch. Dermat. and Syph., 41:521, 1940.
19. Wilson, W. M.: Treatment of Pruritus Vulvae by Alcohol Injection, *J.A.M.A.*, 110:493, 1938.

Effect of Epidemic Gastro-Enteritis on Enterozoic Parasites

By

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ELDERLY, institutionalized persons affected with an acute fulminating para-dysentery were studied at the Philadelphia General Hospital for enterozoic parasites; first for possible etiology, and later, following discovery of bacterial cause, to determine the effect of epidemic dysentery on such parasites.

Several instances have been recorded of amoebic and bacillary dysentery co-existing; and in areas of high incidence of amoebiasis as well as bacillary dysentery,

this dual etiology has been not infrequent. Furthermore, the high incidence of lumen dwelling parasites has made their presence in such dysentery cases comparatively frequent. The effect on the concerned parasites however, has not been well established.

MATERIALS AND TECHNIQUE

This investigation extended over 6 months during which 2-10 (average 4.0) stools were studied macro- and microscopically on each of the 100 afflicted persons. Routinely a Ringer's saline film, a Lugol's iodine film, an iron-alum-hematoxylin stained slide, and concentrated films by both the de Rivas centrifugation and

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the $ZnSO_4$ centrifugal flotation methods were studied.

FINDINGS

Survey Findings. The dysentery was adequately severe to justify an average of approximately 2 months (extremes, 1-3 months) hospitalization. Its rapidly fulminating character prevented pre-diarrhea stool examinations except on 4 patients. These 4 stools were inspissated but otherwise of normal character. One of them contained *E. histolytica* trophozoites and cysts,



Fig. 1.

X 3000

-Crypt produced
by "E. hist."

-Cells of sub-mucosa

R. L. Brown

Fig. 1. *E. histolytica* trophozoite in small mucosal abscess (H & E stain).

another *Giardia lamblia* and *Endolimax nana*. All other initial stool examinations showed no enterozoic parasites. Repeated subsequent examinations during which there were 5-22 diarrheic stools daily on all survey patients likewise were parasite free, except in the *E. histolytica* case (fatal) where 6 of the 7 stools examined had cysts, and 5 of the 6 had trophozoites; and the *Giardia* case in which cysts were present in 3 of

Fig. a

X 300



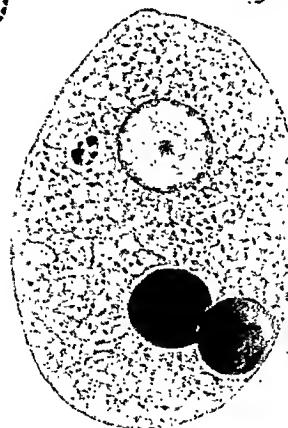
Fig. b

X 3000



Fig. 2

X 3000

-Karyosome
Nucleus-Erythrocytes
(ingested)Fig. 2. *E. histolytica* trophozoite containing ingested materials; drawn from fecal film.

the 8 diarrheic stools, and trophozoites in 2 of the 3. The pre-diarrheic stool contained *Giardia* cysts only; while those during the marked diarrhea stage were parasite free.

During recovery 1-3 inspissated or formed stools were examined on all available patients. These re-

vealed that the previously mentioned case of *Giardia lamblia* and *Endolimax nana* had recovered these lumen dwelling parasites and had added *Endamoeba coli*. Two others previously negative, showed *E. nana* and *Iodoamoeba butschlii* in one and *E. coli* and *Chilomastix mesnili* in the other.

A total of 8 Protozoan parasites were present in 4 of the 100 surveyed persons; only *E. histolytica* could be recovered from markedly dysenteric stools. Five species appeared only in stools from nearly recovered patients. In no instance did the parasites appear definitely cytologically abnormal. However, excessive vacuolization and bacterial ingestion were frequently apparent.

Pathological Findings. The colon, as frequently observed in bacillary dysentery, showed protoscopic and microscopic inflammation. There were ulceration and coagulation necrosis of the mucous membrane. The

Fig. 2a

X 1000

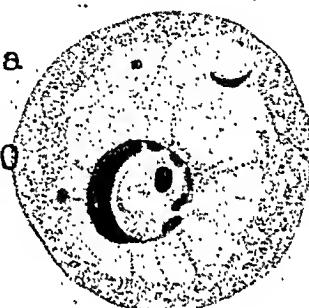


Fig. 2a. Trophozoite with various inclusions; it was recovered from later stool of same patient.

submucosa was edematous and studded with macrophages. Numerous polymorphonuclear leucocytes were scattered throughout the mucosa. The lymphoid structures were slightly involved.

The case with dual infection showed a few characteristic *E. histolytica* microscopic lesions consisting of small mucosal ulcers containing parasites. Such a lesion is reproduced in Fig. 1; Fig. 2 is a trophozoite obtained from one of the dysenteric stools and was stained with iron-alum-hematoxylin.

DISCUSSION

Tissue dwelling enterozoic parasites, i.e. *E. histolytica*, may remain *in situ* in the mucosa during attacks of epidemic gastro-enteritis. Cysts and trophozoites superficially located were apparently dislodged by the peristaltic and purgative action of epidemic gastro-enteritis.

Epidemic gastro-enteritis as well as marked cathartic purgation probably removed many of the lumen dwelling parasites in the second to fifth stools; the remainder were diluted by the hydration of the stools to such an extent that their presence was difficult to demonstrate. *Giardia* were moderately persistent; perhaps due to their abode in the upper intestinal tract.

Marked purgation alone, however, did not eliminate these lumen dwelling parasites. Their presence could be demonstrated again when the stools became formed.

Flagellates, due to their locomotion, were detected earlier than cysts, amoeba and ova.

SUMMARY

1. The effect of acute, fulminating gastro-enteritis on enterozoic parasites was studied in 100 epidemic para-dysentery cases.

2. Bacillary dysentery superimposed on amoebiasis, in one case, showed *E. histolytica* persisting in 6 of the 7 diarrheic stools. Histological slides demonstrated

mucoid diarrhea, but only during early and recovery stages.

4. Endolimax nana, Endamoeba coli, Chilomastix mesnili, and Iodoamoeba butschlii could not be demonstrated in the diarrheic stools of patients parasitized with these organisms. They were present in the formed stools following recovery. This probably accounts for low incidence of enterozoic parasites in epidemic gastro-enteritis cases.

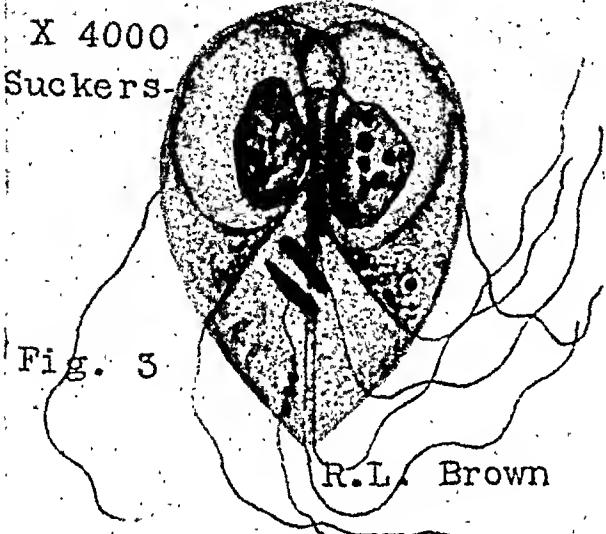
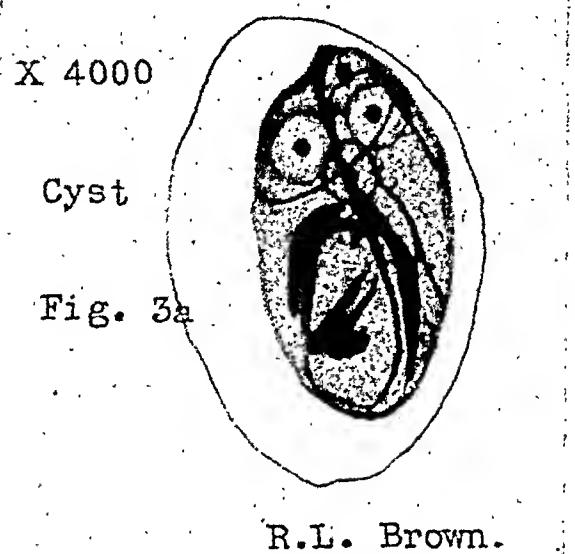


Fig. 3. *Giardia lamblia* trophozoite; and Fig. 3a, cyst, both from paradysenteric stool. Figs. 2-3 are iron-alum-hematoxylin stain. All drawings are reproduced with detailed exactness.

characteristic lesions of both etiological agents in the colon.

3. Giardia were demonstrated in 3 of 8 diarrheic stools. No Giardia was demonstrated during severe



5. The recovered parasites at all stages of the dysentery revealed no abnormal cytological findings. Their persistence or reappearance indicate vital metabolic functions were maintained at a viable level.

REFERENCES

Craig, C. F.: Amoebiasis in Modern Medical Therapy in General Practice, David P. Barr, Ed. Williams and Wilkins, Baltimore, 1940; 2:1830.

Faust, E. C.: Human Helminthology. 2nd ed., Lea and Febiger, 1939.

The Relation of Respiratory Allergy to Unresolved Pneumonia

By

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IT is not generally understood that many affections of the respiratory tract may arise from allergies. Vaso-secretory disturbances of the nasal passages and sinuses, the larynx, the trachea, the bronchi and bronchioles—individually or collectively—may result from sensitizations to various foods, pollens, animal excretions and the like. Such disturbances may be either acute or chronic, or both in succession, and may vary in general character all the way from a good imitation of a "slight cold" to the familiar weeping, wheezing

and general misery known as asthma.

It would not be reasonable to expect that an allergy would appear for the first time following an acute infection in some part of the respiratory tract. However it is perfectly logical that, where allergies have been demonstrated in an individual over a period of time, an aggravated recurrence should follow such an infection and act as a prolonging complication thereto. In both the cases cited herein, this was precisely what happened.

In order to make clear the relation between unre-

solved pneumonia and preexisting allergies, it will be necessary to review briefly some of the general features associated with these various sensitizations.

In many of the cases which have come under my observation the onset has been manifested by tickling of the throat, sneezing and a dry cough. However, some hyper-secretion usually appears very shortly, which may be anything from slight to abundant in amount. In addition to the nasal tract, the conjunctiva may be affected. The secretions of the bronchioles usually cause the greatest discomfort to the patient because of their viscosity and the nature of the cellular and crystalline elements they contain.

I have found such affections of the respiratory mucous membrane, especially vasomotor conditions of the nasal passages, to be a frequent prelude to the development of asthma. The vasomotor manifestations may include itching, tickling, sneezing, "stuffed up" nares. In one case which came to my attention in July, 1939, a man of 43 could not remember ever having been able to breath through his nose, though there was no secretion accompanying the other symptoms. Cutaneous tests were made, a diet of non-allergenic foods prescribed. In just two weeks, the entire condition had cleared up, with normal comfort in breathing for the first time in his life. Now, five years later, there has been no recurrence.

Where the sinuses are involved, as is frequently the case, the mucous membrane may be so thickened that transillumination gives poor results, or none at all. The same applies to X-ray, which may show clear, cloudy or very dull. In either case, the results will vary from one time to another in the same individual, depending upon the vasomotor reaction.

The larynx, when involved, may show edema, especially between the arytenoids. This may take the form of angio-neurotic edema, with the great difficulty in breathing characteristic of this condition.

Where the trachea and large bronchi are affected, there may be no external physical signs, beyond mucous coming up in the throat without a cough. Again this bronchial affection may begin as a troublesome morning cough, with or without secretion or wheezing, or as a dry cough at intervals throughout the day. This dry cough may continue until there is hyperaemia of the bronchial mucous membrane, which, in turn, will give rise to increased secretion. The irritation causing the cough, is often referred by the patient to the portion of the trachea beneath the sternum. This area may feel raw or tender. There may also be soreness in the larynx.

Swelling of the mucous membrane of the bronchioles, from congestion of vasomotor or inflammatory origin, either or both, produces a condition analogous to vasomotor turgescence in the nasal passages, or to urticaria of cutaneous surfaces. Such congestive swelling, in many cases, will cause exudation into the cavity. Swelling in either the smaller or the large bronchi, may arise from vasomotor paresis in its early stages and be followed by inflammation, or it may result from bacterial growth for which this area is highly suitable. Such conditions form the groundwork for asthma.

Asthma, it will be remembered, is due to an irritation of the terminals of the nerves in the respiratory mucous membrane, producing a spasm of the bronchial and respiratory muscles, including the diaphragm. This irritation is caused by allergenic foods, pollens, animal emanations and some other substances. In this class of conditions—including sneezing, occlusion of the nares, sinusitis, angio-neurotic edema, cough and asthma—there is said to be an hereditary predisposition. More correctly speaking, the condition, whether hereditary or acquired, render the patient less able to resist the exciting agents. In asthma, the hereditary tendency, when passed from parent to child, may take the same form, or may appear as some other, related condition.

Asthma knows no age limits. I have seen an infant of nine months, whose asthma had first appeared at four months of age. I have seen asthma appear as late as age eighty-five—and anywhere in between. In both these extreme cases, the asthma disappeared when the foods to which the victims were allergic were avoided.

Gastro-intestinal disturbances, as a corollary to asthma, may either precede or parallel the asthmatic attack. When the asthma is caused by allergenic foods, the digestive symptoms result directly from the same cause. Where allergy is to pollens, animal emanations, or any substances other than foods, the concurrent gastro-intestinal conditions are probably due to inflammation or irritation in the lungs, which in turn, affect the vagus and sympathetic nerves. Many asthmatics however, have these gastro-intestinal symptoms most of the time.

There seems to be a definite relation between the recurrence of paroxysms of asthma and acute lung infections, in that they seldom occur simultaneously. However, after recovery from the acute infection, not only will the chronic asthma reappear, but in some cases, where patients have previously been free of it for years, it will return following such an infection. This appears to be due to the fact that the entire system is rendered more sensitive by the presence of the acute inflammatory products.

Under the terms broncho-pneumonia, lobular pneumonia, catarrhal pneumonia and capillary bronchitis, are included a group of conditions so varied as to cause, and, to a lesser extent, as to pathology, as to suggest that they be called lesions, rather than diseases. From this rather loose list, I would choose broncho-pneumonia as the preferable term, for all affections of this general character.

Broncho-pneumonia, then, is an affection of the lungs in which usually there first appears an inflammation of the smaller bronchioles in scattered areas, succeeded by involvement of anatomically related or contiguous vesicles. In cases of the primary form, the lesions in the two situations may possibly begin more nearly simultaneously, but even here the pathology indicates that exudate first appears in the bronchioles.

Possibly in no other disease do lessened powers of resistance, from whatever cause, play so important a part in determining the inception. This is evidenced

by the wide range of bacteria which, under favorable circumstances may serve as exciting agents of the infection.

The actual pathology and histology of these various forms of pneumonia are so familiar, both theoretically and from practical experience, to every practitioner, that it is scarcely necessary to review them here. For those who wish to refresh their memories, an excellent article by Hobart Hare may be found in Osler's "Modern Medicine," Vol. III, P. 735.

CASE I

May 8, 1922. Male, aged 37. Complained of attacks of coughing, wheezing, which were greatest at 7:30 A. M., lasting fifteen minutes at a time. Sleep undisturbed. Cutaneous tests made and allergenic-free diet prescribed. Symptoms cleared up completely.

November 18, 1931. Coughing, wheezing, shortness of breath, had appeared about five weeks previously. Worst at night. Eczema on back of right hand. New set of cutaneous tests and diet prescribed. Cough, asthma and eczema all cleared up completely.

December 10, 1931. Renewed attack of asthma cleared up as before.

April 15, 1936. Cough, night and morning, with some wheezing. Had appeared two weeks before. Some yellow sputum. Cutaneous tests showed allergy to certain pollens. Appropriate injections given, with complete relief.

February 10, 1937. History of severe pneumonia previous December, under oxygen tent. Following recovery, cough and asthma returned. Dullness, lower left lobe of lung, no air entering. Made another new set of cutaneous tests and prescribed suitable diet. One week later, patient reported he had begun to cough up a dark greyish substance, round in form and two or three inches long—"They look like worms." After five days of this, cough and asthma were seventy-five percent relieved.

March 2, 1937. Dullness of lobe had completely disappeared, air was entering freely, asthma, cough and sputum had completely disappeared.

By adhering to his prescribed diet, this man has remained free of respiratory disturbances up to the present time, now more than seven years.

Here we have a history of recurrent asthmatic symptoms over a period of fifteen years, at intervals varying from ten months to nearly ten years, with an unresolved pneumonia two months prior to the final consultations. At each recurrence, cutaneous tests were made, which gave different reactions each time. I have already shown ("Changes in Sensitivity to Allergenic Foods in Arthritis", American Journal of Digestive Diseases, Vol. II, No. 6, June, 1944, pp. 182-190, Turnbull, John A.) that changes in sensitivity to foods can occur in an individual with the passage of time. This was a case in point. (See also, "Changes in the System Affected by Allergenic Foods," American Journal of Digestive Diseases, to be published.) Suitable diets, varied as the indications changed, produced entirely satisfactory results in this patient.

CASE II

June 23, 1943. Female, aged 57. Referred by patient cited in Case I. Patient complained of cough, sneezing, watery nasal discharge; raising of yellow or greenish sputum which varied in color and consistency; "raw feeling" beneath sternum;

frequent and severe frontal and vertex headaches, both dull and sharp; feeling as of "steam letting off" in both ears; fissures in margins of both nares; eyes sore "like something in them all the time"; itching of face, aggravated by hot weather, washing or rubbing; frequent colds and sore throat during preceding winter; pains in chest, shoulders, lumbar region, knees and ankles in damp or cold weather; perspiring most of the time, especially when walking; very tired in the morning. Cough was of twenty years' standing, recurring in spells every five or ten minutes during the day.

History of pneumonia in April, 1943, followed by increased severity of all symptoms. Examination showed dullness over lower left lobe of lung, no air passing through.

Cutaneous tests were made and allergenic foods eliminated from diet.

July 10, 1943. After one week on new diet, cough was lessened.

July 17, 1943. Sputum had changed from green to light yellow, more mucus raised without much coughing. Over lower left lobe, harsh, rough breath sounds were audible, showing that air was now passing through.

August 11, 1943. Letter from patient stated that, as a result of diet, there was definite improvement in condition, very little cough with slight amounts of thin mucus. In October she reported that cough and mucus had disappeared and she was feeling well.

In this second case also we have the picture of a long history of allergic disturbances, coughing and sneezing, raising of purulent material, cutaneous fissures, conjunctivitis, headache, aggravation of conditions by bad weather; the whole complicated by a recent unresolved pneumonia. And again a diet based on the results of cutaneous tests, brought about a resolution of the pneumonic condition, as well as complete relief of the cough and other long-standing symptoms.

In each of these cases of vasomotor respiratory disturbance, there was fertile ground for a pneumonic condition. The inflammatory vasovagatory condition, following consolidation in the lobe, obstructed release of the exudate from the pneumonic area. It was not until the elimination of allergenic foods from the diet, that removal of the obstruction in the bronchi and bronchioles allowed escape of the exudate from the consolidated area of the lung.

CONCLUSIONS

1. Vasomotor disturbances of the respiratory tract are conducive to bacterial infection, inflammation and pneumonia.
2. Vasomotor disturbances are a factor in obstructing resolution following pneumonia.
3. Use of allergen-free diets may be expected to accomplish resolution in many cases where recovery is complicated by prior existing sensitivities.
4. Two cases of allergic respiratory disturbance combined with pneumonia are reported.
5. One case showed asthma; both, vasomotor rhinitis and cough.
6. Case I showed intervals of recurrence varying from ten months to ten years.
7. Case II showed cough of twenty years standing.
8. In both cases, cutaneous tests were made to determine allergen-free diets, by the use of which resolutions was started within one week.
9. Other symptoms were cleared up in two and four weeks respectively.

REFERENCES

Hare, Hobart A., "Modern Medicine", Osler, Vol. III, p. 735.

Turnbull, John A., "Changes in Sensitivity to Allergenic Foods in Arthritis", American Journal of Digestive Diseases,

Vol. II, No. 6, June, 1944, pp. 182-190.

Turnbull, John A., "Changes in the System Affected by Allergenic Foods", American Journal of Digestive Diseases, to be published.

Book Reviews

Approved Laboratory Technic. By John A. Kolmer and Fred Boerner, Pp. 1018, (\$10.00), New York, D. Appleton-Century Company, Inc., 1945.

The authors have produced what is probably the most up-to-date treatise in laboratory technic in existence today. The material includes microscopy, the care of animals, blood examination, urinalysis, kidney function tests, gastric analysis, liver function tests, pancreas function tests, the examination of spinal fluid and a great deal of space is devoted to parasitology, bacteriology, mycology and virology. In addition to this, serology and methods of preparation of standard solutions and instructions for colorimetric methods are given. Milk and food examinations, toxicology, and complete information respecting the staining of tissues completes a book of erudition and ready reference which no clinical laboratory can afford to be without.

An Outline of Tropical Medicine, By Otto Saphir. Pp. 86, (\$2.00), Chicago, The Michael Reese Research Foundation, 1944.

Our fighting men will be (and in fact already have been) bringing back from South Pacific areas a variety of diseases new to the American physician. It will be up to the physician "to recognize the enemy and to prevent the infiltration or invasion of our citadels of health. Heretofore, the subject has been one of merely academic interest in most of our medical schools and hospitals." But now the staffs of these institutions are faced with the necessity of learning new diseases, and indeed a whole new department of medicine.

It is for such reasons that the present small volume was written. The Outline summarizes the barest essentials of the more important tropical diseases. As an outline it appears to fulfill the purpose adequately. It presents the most pertinent facts clearly and yet avoids the static style so often found in outlines. For the purpose for which it has been designed this volume may well be recommended.

Proteins and Amino Acids. By the Scientific Staff of the Arlington Chemical Company. Pp. 189, Yonkers, N. Y. The Arlington Chemical Company, 1944.

This brief volume was written by the scientific staff of a pharmaceutical company engaged in the manufacture of amino acids for medical use. It is written, however, as a pure exposition of the subject of protein metabolism and is neither biased nor prepared as an elaborate advertisement of a product.

The physiology, pathology and therapeutics of amino acids and proteins are covered briefly. After a short discussion of normal protein metabolism, the role of amino acids, and the functions of plasma proteins, there are presented concise discussions of protein metabolism in pathologic states and the clinical conditions associated with protein deficiencies. A brief account is included of enteral and parenteral therapy with amino acids in various diseases. The book will serve a purpose if it does nothing else than bring to the attention of the general practitioner the subject of amino acid therapy. The degree to which such therapy will be employed in the future is, of course, unknown but the results obtained in war casualties indicate that it probably will be extensive.

The authors of the book succeed in their attempt to present the subject briefly and clearly so that the general practitioner would find it neither too long nor too technical. Each chapter has a select bibliography appended.

Female Endocrinology, with Chapters on the Male. By Jacob Hoffman. Pp. 778 (\$10.00). Philadelphia, W. B. Saunders Co., 1944.

Numerous reviews and volumes on the subject of the physiology and pathology of the female endocrine system have been published. While many of these have been noteworthy contributions to the science, many too have been mere rehashes and poor digests of other men's labors. Not a few of the books had little to commend them except perhaps the quality of the paper used. Dr. Hoffman's volume definitely does not fall into the class of digest literature either requiring or resulting in regurgitation. In this book he has written what appears to be one of the clearest accounts of the female endocrine system, both physiological and clinical. He does not go all out for a "purely endocrine" approach to the endocrine deficiency diseases but considers also the role of non-endocrine factors in the etiology and treatment of the disease. He points out the known facts and emphasizes the difference between knowledge and speculation. Inasmuch as many of women's ills are "functional" and without demonstrable organic basis the psychosomatic aspects of the disease are given some attention. For a concise and understandable account of endocrinology, well illustrated and with a good bibliography included, this book is to be highly recommended.

Abstracts of Current Literature

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

VINSON, P. P.: *Palliative treatment of carcinoma esophagus: report of a case.* (*Virginia Med. Monthly*, v. 72, p. 24, Jan., 1945).

A 74 year old patient suffering from carcinoma of the esophagus had marked dysphagia for about nine months before his first examination. His esophagus was found to be obstructed and there was involvement of the cervical lymph nodes by the tumor. The right recurrent laryngeal nerve was involved and the right vocal cord was paralyzed. Repeated dilatation of the malignant structure was instituted. There developed a definite palliative relief and the patient was able to resume his occupation. Although the carcinoma is still present, the patient, as a result of improved nutrition, is in better condition now than he was when first examined.—B. R. Adolph, Jr.

FISHER, G. E.: *The esophageal manifestations of pellagra.* (*Southern Med. J.*, v. 37, Aug., 1944).

Fisher reviews the literature on pellagra from the date of the first publication referring to the disease in 1725 to the present time. In none of the reports is there a description of lesions of the esophageal mucosa in pellagra patients. The author examined within a two year period seventeen cases of pellagra, ranging in age from twenty-four to seventy-two years. All complained of severe dysphagia. In twelve patients solid foods could not be swallowed, and of these seven could swallow liquids only with difficulty. The usual complaints of anorexia, burning of the tongue and abdominal pains accompanied the complaint of dysphagia.

Each patient presented a characteristic glossitis. In many patients there was an erythematous desquamating dermatitis of the dorsum of the hands, elbows and neck. Conjunctival lesions were seen in a few cases. In each patient the mucosa of the esophagus was found to be intensely hyperemic. Edema of the esophagus was also observed in a few. Multiple erosions or ulcerations of small size were noted in several cases. From three weeks to two months following institution of intensive vitamin therapy all patients were able to swallow without discomfort. The dermatitis and stomatitis also cleared up and the general health was improved.—F. X. Chockley.

TOBENSON, W. E.: *Secondary carcinoma of the esophagus as a cause of dysphagia.* (*Arch. Pathol.*, v. 38, p. 82, 1944).

This report covers 26 cases of secondary involvement of the esophagus by cancer. Nineteen of these cases were picked from 599 consecutive cases of cancer that had come to autopsy. This represents an incidence of 3.2 per cent. Twenty-four of the 26 cancer cases were carcinomas, one was a lymphosarcoma and the remaining one was probably a melanoma. The site of origin of the tumor was: trachea or bronchus (8 cases), stomach (7), larynx (4), breast (2), pancreas (2), and one case each of testis, mediastinum and some unknown site. About 30 per cent of the secondary cancers of the esophagus were due to metastasis from a distant primary tumor. In 12 of the 26 cases there was partial to complete obstruction of the esophagus. In about half the cases there was more or less severe dysphagia.—N. M. Small.

KAHNOLKAR, V. R.: *Oral cancer in Bombay, India. A review of 1000 consecutive cases.* (*Cancer Res.*, v. 4, p. 313-319, 1944).

The incidence of oral cancer in Bombay, India, was studied statistically to determine whether habits, customs, occupational pursuits, and stages of economic development are a factor to be considered. During the 30 months from March, 1941, to September, 1943, 4,765 patients suffering from neoplastic disease registered themselves at Tata Memorial Hospital, Bombay. Out of 2,880 cases of carcinoma the tumor was located in the buccal cavity in 1,000, and in over 60 per cent of these it was situated at the base of the tongue and in the tonsils. Cancer of the cheek, the floor of the mouth, and the alveolus accounted for 22.5 per cent. Cancer of the lips and anterior two-thirds of the tongue was relatively infrequent. Comparison is drawn with a report from the Memorial Hospital, New York, where cancer of the lip accounts for nearly 20 per cent of oral cancer, as contrasted with only 1.7 per cent in Bombay. In New York, cancer of the anterior two-thirds of the tongue is twice as common as cancer at the base, whereas the reverse is true in Bombay. In the Gujaratis (20 per cent of the population), cancer of the buccal mucosa is 6 times more common than among the Deccanis (about 50 per cent of the population), while cancer of the tongue is 1.5 times more

common among the Gujaratis. The incidence of oral cancer in different regions of India has been attributed to the habit of betel leaf chewing. Statistics are given to show that the habitual chewing of betel leaf and areca nut alone has no etiological role in the production of mouth cancer, whereas the addition of some type of dried tobacco powder is closely associated with its development.—Courtesy Biological Abstract.

STOMACH

FIELD, D. D.: *Significance of tubercle bacilli in gastric contents.* (*Am. Rev. Tuberculosis*, v. 50, p. 481, Dec., 1944).

In patients whose sputum is negative or who do not raise sputum examination of the gastric contents has been carried out routinely. The fasting contents are generally used but sometimes the gastric residues brought up by lavage are employed. The use of the guinea-pig test is restricted to doubtful cases only and the culture-tube procedure is relied on almost exclusively since it has been found very accurate. In 868 patients whose gastric contents have been examined at the Sanatorium, 464 patients had positive gastric contents at some or all examinations. It is emphasized that single gastric analyses are not trustworthy if found negative and that five consecutive negative gastric contents be aspirated before the patient is considered negative.—Horace Stilyung.

HINKEL, CHARLES L.: *Hypertrophic gastritis simulating intramural tumor of the stomach.* (*Rad. Ther.*, v. 53, p. 20, January, 1945).

A case of a 32 year old white soldier with discomfort in the epigastrium relieved by eating is reported. This patient had achlorhydria and blood in the gastric contents and roentgenographic evidence of multiple filling defects in the stomach, in the cardia, on the lesser curvature, and in the prepyloric region. Gastroscopic examination disclosed a large thickened irregular ulcerated area on the greater curvature of the proximal stomach; this appeared to be an infiltrative process. The stomach was opened and the mucosa was found to have a raspberry-like appearance. A biopsy specimen showed irregularity of the mucosa and fibrosis of the submucosa, with dilated acini and veins, as well as scattered lymphocytes. A diagnosis of fibrosis and chronic inflammation was made. At Walter Reed General Hospital, a roentgenologic impression of leiomyoma or neurofibroma was based on a lemon-sized circumscribed mass on the posterior wall of the cardia which was fixed, with a stiff wall around the region. Gastroscopic impression was "diffuse benign gastric tumor; possible leiomyoma." At operation, the proximal stomach was found to be adherent to adjacent structures. The microscopic diagnosis was "adenomatoid hyperplasia of the mucous glands with chronic diffuse gastritis." The author presents a brief differential diagnosis of the expected conditions in such a patient, and discusses the gastritides.—Wm. D. Beamer.

HUFFORD, A. R.: *The gastroscope as an aid to diagnosis.* (*J. Mich. State Med. Soc.*, v. 43, p. 1076, Dec., 1944).

The gastroscope is not only valuable for the diagnosis of atrophic gastritis as well as the other gastritides, but is equally important for following the progress of the condition since the atrophic variety may be a forerunner of cancer. Benign peptic ulcer of the stomach is not now thought of as precancerous. It is believed that any malignant ulcer must have been so from the beginning, and all should be watched closely, particularly through the gastroscope. Two per cent of the cases gastroscoped have some form of benign tumor. The combined efforts of the roentgenologist and the gastroscopist should be able to improve the early diagnosis of gastric carcinoma, and together with gastric resection, reduce the 38,000 to 40,000 deaths due to this cause annually. The macroscopic classification of Borrman for gastric cancer should be used by the gastroscopist wherever possible. The four types of gastric cancer are described. The prognosis is governed by the type of growth. Since two to four per cent of the gastric carcinomas are considered multicentric, the possibility of further malignant lesions developing in the remaining portion after gastric resection is enhanced. This of course increases the importance of frequent careful postoperative observations by the gastroscope.—Wm. D. Beamer.

BOWEL

HERBUT, P. A. AND MANGES, W. E.: *Melanoma of the small intestine.* (*Arch. Pathol.*, v. 39, p. 22, Jan., 1945).

Primary melanoma of the small intestine is reported in nine of 25 collected cases of melanoma of the small intestine reported in the recent literature. Among 12 cases of melanoma found in the last 5000 necropsies performed at the Jefferson Medical College Hospital, five were found to be present in the small intestine. Of these, three originated in a cutaneous nervus while the origin of the other two remains in doubt. Melanoblasts were not demonstrated in the small intestine tumor, and the involvement of the small bowel in secondary melanoma is similar to that in which the tumor has been reported as primary. For these and other reasons mentioned, it is thought that melanoma of the small bowel is usually if not always secondary. Sudden colicky pain followed by nausea, vomiting and constipation may be the first and only indication, but anorexia and fullness of the abdomen may be of longer duration. The tumor may be single or multiple, and intussusception often occurs at the site.—Wm. D. Beamer.

CLELAND, J. B.: *The length of the small intestine.* (*Med. J. Australia*, v. 2, p. 359, 1944).

The small intestine exhibits considerable variations in its length, a condition which influences the area occupied by the intestinal mucosa. The influence of the length of the intestine on the individual's physiologic process apparently is not marked and in any event is

at present unknown. The author studied the intestine in more than 100 bodies. The lengths ranged from 13 feet to 37 feet (including only the jejunum and ileum). The size of the individual did not seem to determine the length of his or her intestine. The length of the intestine could not be found to be related to the nature of the disease from which the patient died. Large intestines were found somewhat more frequently in men than in women. The lengths most frequently encountered were 23 feet (in 16 subjects) and 26 feet (in 13 subjects).—M. H. F. Friedman.

BLOOM, H.: *Dysentery in British prisoners of war.* (*Lancet*, v. 2, p. 558, Oct. 28, 1944).

British wounded soldiers captured in the retreat from Tobruk were confined in an Italian hospital under the author's medical supervision. The diet was poor and sanitation worse. In some camps dysentery struck 90 per cent of the men. Starvation and incontinence weakened the men so much that men lay beside the latrines. Transportation of the wounded and ill to Italy was under extremely poor and unsanitary conditions. Endamoeba histolytica was found in the stools but treatment with emetine brought no relief. The persistence of the vitamin deficiency states for long periods in the men after adequate vitamin intake was again restored probably was due to faulty absorption by the bowel because of the atrophy and intestinal ulceration. Diet was very important in the treatment of these chronic bowel affections. Meat was readily assimilated while milk was sometimes harmful. It was found that cathartics should not be given. Sulfaguanidine was found extremely useful.—F. E. St. George.

WEEKS, K. D.: *Intestinal bleeding from ulcerations of Meckel's diverticulum: report of two cases.* (*North Carolina Med. J.*, v. 5, p. 524, Nov. 1944).

Since 1930 Meckel's diverticulum was encountered 45 times at operations at the Duke Hospital. In most of the cases acute appendicitis had been suspected because of the nature of the abdominal pains. Intestinal obstruction and gastrointestinal bleeding were responsible for sending the other patients to operation. A bleeding ulcer of the diverticulum was found in 2 instances. In the case of acute or recurrent periumbilical pain and pain in the lower quadrant the possibility of Meckel's diverticulum should be borne in mind when making the diagnosis. The bleeding from the diverticulum is painless and if it is recurrent the condition should be seriously entertained. Acute and chronic diverticulitis, intestinal obstruction, intestinal perforation with peritonitis, extensive hemorrhage and fistulous tracts are the commonest diseases involving the diverticulum.—F. X. Chockley.

PANCREAS

SAGE, H. H.: *Multiple diffuse pancreatic lithiasis in roentgeno-anatomy of pancreas.* (*Am. J. Roentg. Rad. Therapy*, v. 53, p. 28, Jan. 1945).

The points stressed in paper were that 1) multiple and diffuse calcifications allows for study of the anatomical relationships of pancreas by X-ray, 2) small intestine abnormalities related to pancreatic pathology are seen roentgenologically, 3) the present case represents an early stage in pancreatic dysfunction as indicated by definite changes in the character and content of the stool. Summary of the case report: pain in hypochondria areas which was worse to the right, there was no food dyspepsia and no jaundice, tetany or urticaria. Roentgen examination revealed pancreatic lithiasis in the small bowel. Barium study revealed hypermotility, hypertonicity and coarsening and obliteration of mucosal folds. Serum amylase and lipase values were normal. The stool contained much neutral fat and undigested meat fibres.—Wm. S. Snape.

GLAZER, A. M.: *Pancreatic necrosis in electric shock.* (*Arch. Pathol.*, v. 39, p. 9, Jan., 1945).

Extensive pancreatic necrosis may be associated with fatal electric shock. In non-fatal cases minor changes may occur which should be looked for and treated. Late sequelae to the electric shock are possible, particularly pancreatic insufficiency. Three cases of extensive pancreatic necrosis found in fatal cases of electric shock are presented. In each case most of the pancreas was found to be of normal size and shape but appeared flabby and duller than normal. Various degrees of necrosis were noted and the areas of hemorrhage were likewise variable. In all three cases there was extreme congestion of the central nervous system with perivascular hemorrhage.—Wm. J. Snape.

LIVER AND GALL BLADDER

ELIASON, E. L. AND SMITH, D. C.: *Solitary non-parasitic cyst of the liver.* (*Clinics*, v. 3, p. 607, Oct. 1944).

Solitary nonparasitic cyst of the liver occurs infrequently and up to 1942 the reported literature included 193 cases all told. In 20,000 consecutive autopsies done at the Philadelphia General Hospital prior to January 1944 there were found recorded only 88 cases of nonparasitic cystic disease of the liver. Of these, 39 presented solitary cysts and 49 were polycystic. Only 28 of the cases of solitary cysts were unassociated with cysts in other parts of the body. In no case were symptoms referable to liver cysts presented during life and in each case death was due to some other cause.

The origin of the cysts is obscure but they may represent aberrant bile duct tissue. The clinical features are obscure and diagnosis is difficult. Roentgenologic studies may be helpful. Laboratory blood and liver function tests are of no help. The only treatment, once diagnosis is made or a cyst is found at exploratory operation, is surgery.

Antemortem diagnosis of solitary cyst of the liver was made twice in 211,046 hospital admissions. The authors present the only case ever to be correctly diagnosed preoperatively. Extirpation of the cyst led to the recovery of the two and one-half year old male child.—G. N. N. Smith.

BEESON, P. B., CHESNEY, G., McFARLAN, A. M., AND STEIGMAN, A. J.: *Hepatitis following injection of mumps convalescent plasma.* (*Lancet*, p. 814, June 24, 1944).

An epidemic of mumps occurred in a British regiment in training and passive immunization of tested susceptible subjects was attempted as a prophylactic measure. Convalescent pooled serum was used, taken from the donors usually 7 to 8 weeks after the onset of the mumps, but in some donors a much shorter interval was allowed.

The epidemic declined rapidly but probably the contributory causes were some other than the attempted immunization. Of 226 men who were inoculated and followed, 44.7 per cent developed hepatitis after an interval of 59 to 94 days. About one-third of these men who developed hepatitis had received inoculations with a particular batch of plasma. The incidence of jaundice among 310 men in the same camp who did not receive inoculations was only 1.9 per cent.

The hepatotoxic agent probably was not the virus of infective jaundice. A number of men who had had jaundice previously were also affected. The systemic effects were relatively mild. Vomiting and nausea were rare but loss of appetite was common. Epigastric distress was noted in about one-quarter of the patients. Joint pains were also common. All men showed bilirubinemia on admission, most of them had enlarged livers and conjunctival suffusion. The spleen was palpable in about one-third of the cases. No known etiologic agent was found in feces, blood, throat swabs, and Weil's disease was ruled out by serological tests.—F. E. St. George.

JONES, M. J. AND PECK, W. M.: *Incidence of fatty livers in tuberculosis with special reference to tuberculous enteritis.* (*Arch. Internal Med.*, v. 74, p. 371, 1944).

A study was made of the findings in routine autopsies carried out on tuberculous patients. Of 581 such autopsies fatty livers were found in nearly half the number (41.9 per cent). A constant finding in all the cases of fatty liver was that of emaciation. In patients showing tuberculous enteritis there was a closely associated finding of extensive fatty infiltration.—N. M. Small.

GILLMAN, J. AND GILLMAN T.: *The liver in pellagra.* (*Lancet*, v. 247, No. 6309, p. 161, 1944).

Biopsy specimens of the liver were taken on patients presenting symptoms of pellagra or other nutritional diseases. In pellagra the liver damage consisted of widespread deposition of fat. In adults this may be followed by deposition of cytosiderin, an iron-containing pigment, and give rise to a condition of pigment cirrhosis. The fat may be caused to be reabsorbed by appropriate diet therapy. Pigment cirrhosis has been encountered clinically only in man and has not yet been duplicated in animals by dietary experimentation. The authors did not observe any signs of necrosis of the liver or of hemorrhage even tho the patients had

been on prolonged low protein intake.—F. E. St. George.

KENNAWAY, E. L.: *Cancer of the liver in the negro in Africa and in America.* (*Cancer Res.*, v. 4, p. 571, 1944).

An attempt is made to compare statistical data relating to the incidence of cancer of the liver in Negroes in Africa and in America. The survey suggests that the very high incidence of primary cancer of the liver (90.5 per cent of carcinoma cases) found among Negroes (Bantu laborers) in Africa does not appear among Negroes in the United States. Therefore, it is not considered a purely racial character, but perhaps one related to environment, or genetic susceptibility to an environmental factor. The statistical evidence is confused by the inclusion of cancer of the gall bladder in the same category with cancer of the liver.—Courtesy Biological Abstracts.

JOHNSON, W., MALSTROM, B. E., AND VOLK, B.: *A clinico-pathologic study of 100 cases of acute and chronic gall bladder disease.* (*Ann Intern. Med.*, v. 94, p. 431, Sept., 1944).

The patients sampled were 19 males and 81 females. The average age was 46.4 years. Seventy-one had calculi. Etiology of gall bladder disease may be by numerous routes: ascending infection from the duodenum, by the hepatic route, via portal route, direct extension from an infected organ or by the lymphatics, and pregnancy.

Symptoms are the same whether the disease is acute or chronic, calculous or non-calculous. The degree of severity is the only difference. The Graham-Cole test must be properly evaluated since the error may be in either direction.

The pathology was found to consist of inflammation which was not always proportional to the clinical picture. The epithelium usually showed no change. Lymphocytic infiltration was no criterion. Thickening of the gall bladder may have been due to fibrotic replacement of the muscular and elastic tissue. The majority of the thickening was caused by edema of the sub-serosa. The sub-serosa in hydrops was atrophic and infiltrated. Empyema was studied in four cases. Cultures were negative in two and *B. coli* and *Staphylococci* were found in the other two. Inflammation brought on by acute obstruction of the cystic duct was manifested by edema in the outer coats along with infiltration of the subserosa. Follow up of the cases showed non-calculous cholecystitis to be handled better by medical means and the calculous cholecystitis to be handled better by surgery.—Wm. S. Snape.

EISS, STANLEY: *Jaundice: Surgical considerations.* (*Am. J. Surg.*, v. 47, p. 23, January, 1945).

A history of biliary colic is usually obtained in obstructive jaundice and is the main factor pointing to a condition requiring surgery. Chills, fever, light-colored stools, and rigidity and tenderness may or may not be present. Since it may be impossible to determine the

type of jaundice clinically, laboratory aids such as X-ray studies and chemical tests are essential. All the tests are based upon certain functions of the liver, but even these at times may not be helpful. In case of doubt, a preliminary period of four to six hours for parenteral support is necessary before operation, and this period can be prolonged in a less acute case. Repeated laboratory tests are made to measure any changes or degree of persistency of the condition while under conservative treatment. The author believes that the qualitative Van den Bergh test is of value in differentiating obstructive jaundice from the other types.

—Wm. D. Beamer.

ULCER

MEISELAS, L. E. AND RUSSAKOFF, A. H.: *Bleeding peptic ulcer in infancy.* (*Am. J. Dis. Child.*, v. 67, p. 384, 1944).

Peptic ulcer in infancy is uncommon and bleeding peptic ulcer is rare. The case is reported of an infant age two and one-half months who presented symptoms that were misleading. There was no history of hematemesis. Progressive anemia, a raised blood urea, projectile vomiting and occult blood in stool were indications of an ulcer. However, diagnosis was not made until just prior to death because until then dietary difficulties were believed responsible.—I. M. Theone.

THERAPEUTICS

MAKAROV, J. V. AND KHAIN-MAKAROVA, G. A.: *Treatment of gastro-intestinal disorders with sodium zosterate.* *Pediatriia (Moscow)*, v. 1944, p. 53-57, 1944).

Zosteric acid was isolated by A. I. Vedrinskii from the seaweed *Zostera nana* and was found to be a pectinic acid-like polygalacturonic acid. The sodium salt was used: 1) as a 2 per cent solution (the dry powder dissolved and 5 per cent sugar added); 2) as a brei (cereal) containing 1-2 per cent of the powder, 5-10 per cent cream of wheat and 10 per cent sugar. One hundred fifty to two hundred cubic centimeters of the cereal were given 2 to 3 times a day for 3 to 4 days. Some of the children did not like it, so pear essence had to be added for flavoring. Of 63 children treated, 46 were less than 2 years old. There were 15 patients with simple dyspepsia, 14 with subtoxic and toxic dyspepsias, 12 with dysenteries, 4 with enteritides and 18 with chronic enteritides. One patient with toxic dyspepsia and 2 with dysenteries have died. The rest of the children have reacted nicely to the treatment. Recurrences were noted in some of the chronic cases and the treatment had to be repeated.—Biological Abstracts.

IVY, A. C., GROSSMAN, M. I., AND GUTMANN, M.: *The effect of aloes and podophyllum (resin) (Carter's Little Liver Pills) on the output of bilirubin and cholic acid in human duodenal drainage fluid.* (*Quart. Bull. Northwestern Univ. Med. Sch.*, v. 19, p. 37, 1945).

Eight normal male and one female human subjects ages 22 to 40, were studied. Each was given either

four Carter's Little Liver Pills or else saline. Duodenal drainage continued for four hours. The results of the analyses of the duodenal drainage fluid were compared also with those obtained during a two hour period before the subjects were given the pills.

The results showed that the pills did not increase, within four hours, the volume of duodenal drainage, or output of bilirubin or output of cholic acid over the amounts obtained in response to physiological saline solutions alone.—D. A. Wocker.

OSETRINKA, M. S.: *The influence of nut milk and Jidda brew upon diarrheal conditions and upon the functions of the gastro-intestinal tract.* (*Pediatriia (Moscow)* v. 1944, p. 49, 1944).

Twenty-five grams of walnuts were soaked in boiling water, ground, boiled in one liter of water, strained through gauze and 5 per cent sugar added. One hundred and fifty grams of this milk was given 3 times a day to breast-fed infants, or 800 grams daily for 3 days when no breast milk was available. Four hundred grams of Jidda (a shrub belonging to the Elaeagnaceae) fruits, which were found to contain much tannic acid, were soaked in one liter of boiling water for 12 hours, boiled, the kernels removed, strained through a sieve and both 5 per cent starch and 5 to 7 per cent sugar added. The resulting brew did not look nice, but the babies seemed to accept the taste of it, and 150 grams were given 1 to 2 times daily. Forty-four children less than 2 years old were treated. Of these, 7 had simple dyspepsia, 12 were subtoxic, 10 had toxic dyspepsia and 15, colitis. Improvement of stools and symptoms were reported in all patients; some of the very toxic however, did not react at all. Gastric and duodenal juice tested showed a gradual increase in the enzyme content.—Biological Abstracts.

AARON, A. H.: *Comment on drugs frequently used in the treatment of gastro-intestinal conditions.* (*Clinics*, v. 3, p. 663, October, 1944).

Aaron reviews the products most commonly prescribed or used for diseases of the digestive tract as shown by the number of prescription, hospital orders and physicians' dispensed products. Sodium bicarbonate, magnesium oxide and calcium carbonate are the alkalis most frequently used. Sodium bicarbonate is not as popular today as it was in the past because of alkalosis and rebound gastric secretion. Calcium carbonate tends to be constipating. Kaolin, charcoal and aluminum hydroxide are the commonest adsorbents. The one drawback with aluminum hydroxide is its tendency to produce obstipation with fecal impaction, a fault which is corrected by administration with mineral oil. Milk of bismuth is the substance Aaron found to be used most often as a protective coating of the gastrointestinal tract. Aaron thinks milk of bismuth to be inferior to bismuth subgallate, subcarbonate or subnitrate as a protecting cover substance. Hydrochloric acid is popular in the treatment of achlorhydria but the amount given usually is quite inadequate. Belladonna was found to be prescribed most

often in combination with a sedative but Aaron thinks this is incorrect therapy since it does not permit manipulating the dose of belladonna without corresponding changes in the dose of sedative. To stimulate bile flow ox bile is recommended and dehydrocholic acid is suggested for increasing the water content of biliary secretion. The Boyden test meal or dried egg powder is used to evacuate the gall bladder.

Aaron presents typical prescription for the various products discussed and comments on their value. He points out the fallacy in assuming that the number of minimis of a liquid can always be measured by counting the number of drops. Thus he found that there were 22.2 drops of distilled water, 50 of alcohol, 50 of belladonna and 28 of 50 per cent solution of potassium iodide to a cubic centimeter of each.—G. N. N. Smith.

SURGERY

REINBERG, S. A.: *X-Ray diagnosis in gunshot wounds of abdominal cavity and its significance in field surgery.* (*Brit. J. Radiol.*, v. 17, p. 291, Oct., 1944).

Before the war correct diagnosis was obtained by roentgenologic means in over 90 per cent of the cases of perforated gastric and duodenal ulcers and acute intestinal obstructions. Roentgen investigation of abdominal injuries in war time is important and should be made calmly and without undue hurry. Shock is no contraindication to such procedure. The wounded patient is not removed from the stretcher and is never made to stand. No contrast substance is given internally if the stage is acute. Not only is the abdominal cavity X-rayed but the chest and pelvis must also be included.

Most of the wounds were penetrating wounds; perforating wounds were few and tangential wounds were fewer still. Entry to the abdomen was in half the cases thru the lower part of the chest, next in frequency came the pelvis as a route of entry.

The most important wound is one which perforated the gastrointestinal tract. Escape of gas or fluid from the viscera should be sought for. Pain in the region of the shoulder is often associated with pneumoperitoneum. Gas escaping from the gut and covering the liver reduces the dullness of the liver to percussion. As soon as gas is demonstrated in the abdominal cavity the patient should be operated.—F. E. St. George.

EXPERIMENTAL MEDICINE

MOTILITY

AUER, JOHN AND KRUEGER, H.: *Motor analysis of anti-peristalsis in the descending colon of rabbit.* (*Proc. Soc. Exp. Biol. Med.*, v. 57, p. 360, Dec., 1944).

Under barbital anesthesia the colon of rabbits was exposed and peristaltic activity observed directly. Introduction of a dry scybalum one to two centimeters into a segment of colon produced a peristaltic contraction. If the progress of the scybalum was presented in the colon by digital compression of the segment, the peristaltic wave ceased and its direction was reversed to become an antiperistaltic wave of compression. The speed of an antiperistaltic wave was much slower than that of a peristaltic wave. The same conditions hold

for antiperistalsis as for peristalsis: the wave of contraction is preceded by a wave of relaxation. No clear-cut antiperistalsis of the colon was observed when the spinal cord had been pithed and both the splanchnic nerves and the vagi had been severed.—M. H. F. Friedman.

ABSORPTION

BUCKER, G. R., FLYNN, J. C. AND ROBINSON, J.: *The action of the human small intestine in altering the composition of physiological saline.* (*J. Biol. Chem.*, v. 155, p. 305, 1944).

The study was carried out on eighteen healthy human subjects. Physiological saline was introduced into the small intestine and samples of intestinal contents withdrawn at varying intervals. Measurements of chloride concentration, bicarbonate, total base and pH were made on the samples. As the samples passed from the duodenum to the ileocecal valve they progressively increased in pH and bicarbonate content. The chloride content decreased and the total base remained unaffected.—M. H. F. Friedman.

PATHOLOGY

ENDICOTT, K. M., DAFT, F. S., AND SEBRELL, W. H.: *Dietary cirrhosis without ceroid in rats.* (*Proc. Soc. Exper. Biol. Med.*, v. 57, p. 330, Dec., 1944).

Rats on a purified diet low in protein and in choline develop hepatic cirrhosis. The cirrhosis is always accompanied by an insoluble pigment which is deposited in the trabeculations of the liver and to which the name "ceroid" has been given. The ceroid may be peculiar to the rat since it has not been observed in experimental hepatic cirrhosis produced in the dog, guinea pig, rabbit and pig and has not been found in the human. In the present experiments the attempt was made to determine whether in the rat the presence of ceroid was an essential feature of liver cirrhosis. Certain purified diets were fed which led to liver cirrhosis with ceroid. It appears likely that ceroid deposition in the liver is induced by feeding cod liver oil. Palmitic, stearic, oleic, linoleic, and linolenic acids did not lead to ceroid deposition. The nature of the substance or substances in cod liver oil is unknown. Final proof of the independence of ceroid from cirrhosis is the development of cirrhosis in rats kept on a completely fat-free diet.—M. H. F. Friedman.

DOLJANSKI, L. AND ROSIN, A.: *The histology of the rat's liver in urethane poisoning.* (*Am. J. Pathol.*, v. 20, p. 945, 1944).

Studies of the injury to parenchymal cells and vascular structures in particular were made on rats that received either single or repeated injections of urethane. In large amounts urethane led to extensive damage of the sinusoidal capillaries and portal veins. This damage resulted in extravasation of plasma and cells thru the walls of the blood vessel. Hydropic degeneration was the main type of injury to the parenchymal cell and was relatively slight. The liver cells in the central parts of the lobule atrophied and disappeared after prolonged action of urethane. The injury to the

parenchymal cell may have been due either to direct action of the urethane or have resulted indirectly as the result of the damage to the vascular system in the liver.—N. M. Small.

KERKAMP, H. C. H.: *Gastric ulcer in swine*. (*Am. J. Pathol.*, v. 21, p. 111, Jan., 1945).

Ulcers similar in morphologic characteristics to the gastric or peptic ulcers in man were observed in swine on eighteen occasions. At no time did these ulcers give rise to symptoms. This disease in swine was found in this study of 754 animals to have an incidence of 2.38 per cent. However, this figure covers a special study on ill animals; the actual incidence in the general swine population is unknown. Eight of the eighteen pigs were males; all were less than one year old. Altho no satisfactory explanation for the specific and definite cause of the ulcers can yet be advanced, there would appear to be some casual relationship to the occurrence of nutritional anemia.—M. H. F. Friedman.

MARSHAK, A. AND WALKER, A. C.: *Mitosis in regenerating liver*. (*Science*, v. 101, p. 94, Jan. 26, 1945).

Mitosis after partial hepatectomy in one-month old rats is at a maximum 24 hours after operation. A number of substances were administered intravenously 24 hours after operation with the view of determining whether they had any effect to further increase the rate of liver regeneration. Chromatin prepared from rat liver was found to contain some factor which increased the rate of mitosis of liver cells by 25 to 100 per cent. Chromatin prepared from beef liver increased mitosis by 70 per cent and that prepared from rabbit liver increased mitosis by 55 and 290 per cent.

Nuclei of regenerating liver cells incorporate radioactive phosphorus more rapidly from fat-free chromatin than from phospholipid or inorganic phosphate. Change in the chromosome composition by such a process may account for gene mutations.—M. H. F. Friedman.

PATHOLOGY CHEMISTRY

KORNBERG, A., DOFT, F. S. AND SEBRELL: *Mechanism of production of vitamin K deficiency in rats by sulfonamides*. (*J. Biol. Chem.*, v. 155, p. 193, 1944).

The authors show that the synthesis of vitamin K by intestinal bacteria can be inhibited not only by giving a sulfa drug (sulfadiazine) by mouth but also by administering the drug subcutaneously. The vitamin K concentration in the cecal contents and in the feces is reduced by either oral or subcutaneous administration of sulfadiazine to an extent proportional to the amount of the drug. Complete absence of the vitamin can be attained. Para-aminobenzoic acid given subcutaneously will reduce the anti-vitamin K effect of sulfadiazine. Vitamin K deficiency resulting from the sulfadiazine is due to depression of its synthesis by intestinal bacteria as the result of interference with bacterial metabolism.—G. Klenner.

BEVERIDGE, J. M. R., LUCAS, C. C., AND O'GRADY, M. K.: *The effect of the nature and level of protein and amino acid intake on the accumulation of fat in the liver*. (*J. Biol. Chem.*, v. 154, p. 9, 1944).

Rats were kept on a basal diet deficient in tryptophane, valine, isoleucine and threonine and their liver fat content determined. The liver fat was greatly reduced when methionine in the free form of amino acid was added to the basal diet. However, methionine provided by the addition of casein to the diet did not have as good a lipotropic action. Addition of tryptophane, valine, isoleucine and threonine (obtained from casein hydrolysis or as the pure amino acids) to the diet abolished the difference in lipotropic action of the two forms of methionine.—G. Klenner.

BEAMS, A. J., FREE, A. H. AND LEONARDS, J. R.: *Experimental hypoproteinemia: studies on intestinal absorption and intestinal roentgenologic characteristics*. (*Arch. Internal Med.*, v. 73, p. 897, 1944).

By means of the plasmaphoresis technique hypoproteinemia with edema was produced in dogs. The rates of intestinal absorption of galactose and glycine were not affected by the hypoproteinemia and edema, nor were gastric emptying time or intestinal motor activities influenced. Unaltered also was the rate of metabolism of glycine and galactose.—G. N. N. Smith.

MISCELLANEOUS

CAGO, M.: *Glycogen storage disease; case report*. (*Arch. Dis. Childhood*, v. 19, p. 181, Dec., 1944).

A male child, age three and one half months, was admitted to hospital with symptoms of projectile vomiting and attacks of hypoglycemia. Autopsy showed little gross pathology but microscopic examination of various tissues showed the liver cells, heart (left ventricle), renal tubules, epithelial cells, duodenal villi and mucosal glands to be laden with glycogen.

Glycogen storage disease would appear to be congenital since it becomes apparent at birth or soon thereafter. Projectile vomiting may perhaps be explained by the accumulation of glycogen in the pylorus, thus resulting in pyloric stenosis.—E. R. Feaver.

NASIO, JUAN: *A test for gastric function using 2-Benzol-imidozoline orally*. (*Anal. Dispens. Publico Nacion, Enfermed. Aparat. Digest*, v. 6, p. 127, 1943).

In Nasio's opinion there are three distinct disadvantages to the use of histamine as a test of gastric secretory function. The drug must be administered only parenterally and can not be given orally, histamine has numerous side-reactions, and certain patients may at times be histamine resistant. The compound recommended by Nasio can be given by mouth and it appears to be without side actions. Included in the paper are two tables illustrating typical gastric secretory responses to the drugs in various patients. The technique employed is discussed.—D. J. Abolafia.

Some Biologic Considerations of Gallstones

By

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ONE of the annoying experiences in the treatment of biliary disease is to have a patient develop biliary colic subsequent to the removal of a gallbladder which had contained stones.

Obviously either all of the stones had not been removed by the cholecystectomy or else the mechanism of gall stone formation had not been eradicated by the operation and remained intact to function again forming additional stones which gave rise to symptoms at a subsequent period.

This raises the question of the mechanism of gallstone formation and their tendency to occur in some individuals.

PRESENT CONCEPTION OF GALL BLADDER FORMATION

Gall stone formation is not a simple devise. It probably involves several mechanisms working simultaneously and each of these methods is an involved process.

Certain factors are at present accepted as operating in the formation of gall stones. These are (1) infection, (2) changes in the composition of bile, (3) bile stasis.

Infection.—Most writers agree that infection plays an important role in the formation of gall stones (Gaither (1), Lichtman (2), Karsner (3), Walters and Snell (4), etc). In support of this view it is pointed out that bile is brought to the liver by the blood which may also carry bacteria, likewise bacteria may enter by the ascending route from the intestine. In either case it is the function of the bile to render the bacteria harmless. Nevertheless such organisms, even though they have been made inert remain to form a nidus about which the bile salts collect and so form concretions. Not all bacteria entering the biliary tract become sterilized. In a certain percentage of people the organisms reach the wall of the gall bladder to set up an infection and produce a cholecystitis. Within the walls of these infected gall bladders, the organisms may remain viable; likewise the organisms may also remain viable in the bile of some gall bladders. When a gall bladder becomes infected, the functions of the mucosa become altered with a resulting interference in the behavior of the bile within the gall bladder. Thus there results changes in the concentrating power, in the secretory function and absorbing power of the gall bladder.

It has long been known that cultures made on the bile removed at the time of operation, the so called "operative bile" yield pathogenic bacteria frequently, while cultures made from the wall of surgically removed gall bladders yield even a higher incidence of cultures of pathogenic bacteria.

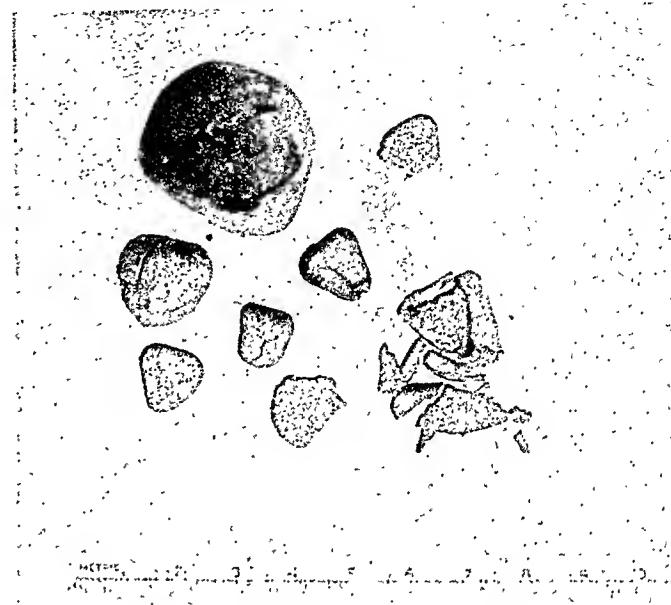


FIG. 1—ANIMALS HAVE GALL STONES.

Stones from the gall bladder of a ten year old cow of multiple pregnancies.

Rosenow (5) was one of the first to record his observations on the bile obtained at the time of operation. In 1916 he recorded that fifty-one percent of cultures made by him yielded positive growths in which the streptococcus predominated. Among the other organisms were found *B. Coli*, *B. welchii*, *B. proteus*, and diphtheroids. In 1924 Blalock (6) reported that fifty-eight percent of his series of 270 specimens of operative bile gave positive cultures in which *B. coli*, *staphylococcus*, and *B. typhosus* were the predominating organisms. In 1935 Hanssen and Yurevich (7) made an exhaustive study of the literature on the bacteriology of the bile adding their own study of 104 patients with chronic cholecystitis. In their patients studies were made on both the bile and the gall bladder wall. They obtained positive cultures in thirty-three percent of their studies. The wall of the gall bladder was the site of viable pathogenic organisms more frequently than the bile.

Twiss (8) considered that in making a bacteriologic examination of the bile, the procedure is exposed to contamination by oral and gastric contents, so he undertook to avoid these hazards of contamination by devising a special duodenal tube with an encapsulated opening to prevent such contamination. With this method, he studied 120 patients in whom a cholecystectomy was subsequently performed. With these elaborate precautions he obtained positive cultures in twenty-eight of his cases of preoperative bile who yielded pathogenic organisms.

Another factor operating in infection is the increased secretion of mucus by the mucosa which occurs when it is inflamed or irritated. This is apt to disturb the chemical balance of the bile.

Changes in the composition of bile.—Alterations in the composition of bile is regarded as contributing to the formation of stones.

Normally ingested cholesterol is absorbed by the intestine into the lymph stream after hydrolysis by the pancreatic and intestinal enzymes. However it is resynthesized into cholesterol before reaching the blood stream. Some cholesterol is normally excreted into the bile for ultimate elimination from the body (Best and Taylor (9)). In both the liver and gall bladder, the cholesterol of the bile maintains a definite ratio with reference to the bile salts. This ratio is one part of cholesterol to 20 to 30 parts of bile salts. The solubility of the cholesterol seems to depend upon maintenance of this ratio. If the ratio falls to 1:13 or less, precipitation of the cholesterol results.

Some writers state that when cholesterol of the blood becomes increased, it becomes secreted in increased amounts in the bile. This is suggested by the high incidence of gall stones in pregnancy, obesity, starvation, high fat diets, hemolytic jaundice and other disorders in which a high cholesterol content of the blood is apt to occur with a subsequent increase in the cholesterol content of the bile.

Andrews (10, 11) and his associates believe that when infection is present it plays its part in gall stone formation not so much through increased cholesterol production, rather through the reduced bile salt concentration which he believes are lost by excretion through the inflamed gall bladder walls.

Dolkart, Jones and Brown (12) attach more importance to the concentration of fatty acids in the bile than to the bile salts in preventing the precipitation of the cholesterol. Likewise Walsh and Ivy (13) support this view stating that their results indicate that the soap-cholesterol ratio in the bile is very important and that an optimum concentration of soap is necessary for the solution of human gall stones when placed experimentally in the gall bladders of dogs.

Exner and Heyrovsky (14) have pointed out that precipitation of cholesterol is also favored by the bacterial action taking place within the bile salts, also by a change in the pH of the bile when it swings to the alkaline tide.

Irrespective of the immediate precipitating factor, whenever the balance of the cholesterol of the bile is disturbed, cholesterol becomes precipitated and gall stones are formed.

Biliary stasis.—Biliary stasis plays an important role in the formation of stones. Biliary stasis gives rise to an altered flow or composition of bile and so provides the initial changes to favor the formation of stone by decreasing the dissolving power of the bile for cholesterol. During stasis the resorption of water by the wall of the gall bladder continues in spite of the stasis, thus further increasing the concentration of the bile to the saturation point when precipitation is apt to occur.

Clinically this is supported by the observation that those conditions in which stasis is apt to occur as organic heart disease, overweight, pregnancy, debilitating states, sedentary habits, etc., are apt to be identified with the presence of gall stones.

The high incidence of gall stones in pregnancy has been correlated with various factors including the high cholesterol content of the blood, high cholesterol content of the bile, the low bile salt content of bile; the distention of the gall bladder, the delayed emptying time of the gall bladder, interference with the normal concentrating function of the gall bladder.

The high incidence of gall stones in women who have been pregnant is often cited as indicating that a causal

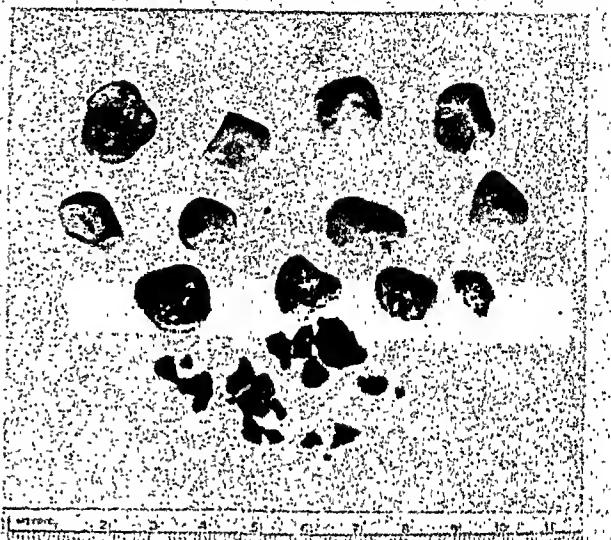


FIG. 2.—SOME FAMILIES HAVE A HIGH INCIDENCE OF GALL STONES.
Gall-stones from an unmarried woman whose unmarried sister, their mother and maternal grandmother also had gall stones.

relationship exists between a high cholesterol content of the blood and its resultant increase in the cholesterol content of the bile and the subsequent formation of stones.

Indeed some writers declare that ninety percent of all women who have gall stones have also had children. This view is by no means universally accepted. Robertson and Doucet (15) state that from their studies of the literature it would appear that pregnancy is not the major cause that it was supposed to be in the causation of gall stones in women. Nevertheless they do agree that women are more prone than men to have gall stones and that gall stones occur in women at an earlier age than in men.

Hypercholesterolemia is often cited as the immediate cause of gall stone formation, yet this view has not been proved according to Karsner (3), who states that the two do not occur at the same time. He points out that although stones do occur in women who have been pregnant and hypercholesterolemia is common in pregnancy, that years may elapse before gall stones are observed. On the other hand both men and women have gall stones without any proof that they ever have had hypercholesterolemia.

Karsner (3) however stresses the importance of biliary stasis. He states that "stagnation of bile is followed by concretion." He points out that stasis may be due to diseases of the gall bladder or its ducts, to delayed emptying time of the gall bladder, to sedentary habits, as well as other pathologic states, inflammatory or otherwise which interfere with the normal emptying time of the gall bladder. He points out that inflammation of the gall bladder thus plays a double role. First the inflammatory process causes an increased exudate into the bile which alters the chemical balance of the bile and second the inflamed wall of the gall bladder loses its normal absorbing power. Both of these favor the precipitation of solids from the bile and the formation of stones. When stones are formed they in turn irritate the wall of the gall bladder and incite further inflammation, and so a vicious cycle is formed.

Most writers give the impression that stasis of the bile occurs frequently, that it is not necessary to have some gross pathologic lesion to cause biliary stasis; rather it can be caused by numerous minor functional disturbances of the gall bladder or it may result from some systemic condition nothing more serious than sedentary habits, pressure from contiguous organs, debilitating states, obesity, pregnancy, as well as inflamed gall bladders.

The formation of pigment stones and calcium deposits follows the same general principle of disturbed chemical balance within the bile as that manifested by the mechanism of cholesterol precipitation.

In light of existing knowledge it may be stated that the formation of gall stones begins with a nidus or nucleus which is provided by an inflamed gall bladder or bile duct; that the inflammation is probably bacterial in origin; that about these nuclei are precipitated cholesterol, bile pigments or calcium salts whenever the mechanism which holds these in suspension in the bile is disturbed; that there exists a definite ratio between the cholesterol content of the bile and the bile salts; that this ratio is one part cholesterol to 20 to 30 parts of bile salts, and whenever the ratio falls to one part of cholesterol to thirteen parts or less of bile salts, then cholesterol is precipitated and stones are formed; that a somewhat similar mechanism operates to cause the precipitation of calcium and pigments. If this view is tenable then there is no reason why gall stones cannot form after the gall bladder has been removed since the mechanism is independent of the presence of a gall bladder, rather it is confined to the chemical mechanism of the biliary system and not to the anatomic structure of the gall bladder.

HUMAN INCIDENCE

The occurrence of gall stones is universal in the human race as far as we know. It exists among all races of all climates. No group is immune. No segment of society escapes the excruciating pain of its colic. Economic factors and income however do influence its occurrence to the extent of proving a high fat diet and the oppor-

tunity for sedentary habits for those who would enjoy indulgent living; likewise race seems to have some influence in its incidence.

Robertson and Duchat (15) report that an analysis of over 100,000 cases examined postmortem 12.7 percent of the females had gall stones and 5.7 percent of the males had stones. Lichtman (2) states that the incidence of gall stones in the adult population of this country based on necropsy findings is estimated at from 5 to 20 percent while in Sweden it is 10.5 percent; however a lower incidence exists in certain parts of the world where life is more strenuous and the diet is frugal and largely vegetarian, as in Russia, India and Japan. Ludlow (16) finds that the negroes of the Cleveland area have a slightly lowered incidence than their white neighbors. The whites had an incidence of 8 percent whereas the negroes had only about 5 percent.

Women have a higher incidence than men; likewise stones occur in an earlier age group in them than in men.

There is no evidence that gall stones is a recently acquired disease by the human race. Indeed its history goes back to the earliest writings. The first known mention of human gall stones was made in the fifth century by Alexander of Thralles (17) who wrote of "dried up humors concreted like stones" which he thought had some influence on "obstruction of the liver."

BIOLOGIC INCIDENCE

If gall stones were a purely human problem the study would end with the description given by Alexander of Thralles in the fifth century. However the problem is much wider than that. Gall stones not only exist among all known races, but they exist in numerous other species of the animal kingdom.

In 1932 Gauss and Davis (18) working in the Department of Medicine at the University of Colorado and the Bureau of Animal Industry of the U. S. Department of Agriculture investigated the incidence of gallstones and other incidental cholecystic disease encountered in the routine examination of animals slaughtered for human consumption in a packing house of Denver. They examined the carcasses of 2067 unselected cattle. In these they found gall stones in 21 animals or a little over 1 percent. Of the 21 animals, 17 were adult cows that had born calves and of these 8 were pregnant at the time of slaughter. One lone bull was found to maintain the honor for his sex, while steers (emasculated bulls) made up the remainder.

Although heifers (adolescent females) comprise the largest group, there were no instances of gall stones among them suggesting that they had not reached the age group favorable for their appearance. The highest incidence occurred in cows suggesting that pregnancy is an important predisposing factor.

The age incidence of Gauss and Davis series of cattle varied from 2 to 10 years with an average age of 6 years which represent middle life for cattle.

Incidence of Gall Stones in Cattle

(Gauss and Davis Study of 2067 Animals)

	Cows	Heifers	Steers	Bulls	Total
Animals examined	753	917	316	81	2067
Animals having stones	17	0	3	1	21
Percentage	2.3%	0%	1.0%	1.2%	1.0%

In addition to the presence of gall stones, Gauss and Davis observed the following gross pathologic lesions: five gall bladders contained papillomatous nodules in the mucosa, one contained several small reddened plaques in the serosa probably the result of fluke infestation, one gall bladder contained 2 small diverticula, while one gallbladder was thickened and markedly indurated being adjacent to a liver abscess.

As to the location of the stones, 17 animals had the stones in the gall bladders while in four, they were found in the bile ducts.

Another observer to report the presence of gall stones in cattle is Totten (19) who reports an incidence one half of one percent in a series of 5725 cattle.

Stones according to some reports also occur spontaneously in hogs. Pigment stones occur occasionally in dogs. Schlotthauer and Stalker (20) report two cases.

For some time it was believed that gall stones could not be produced experimentally; nevertheless Meyer, Nielson and Feusier (21) did produce them in rabbits which had been injected with typhoid bacilli. When a chronic cholecystitis resulted from the intravenous injections, the development of stones was favored.

On the other hand, the amazing observation had been made by Dolkart, Jones and Brown (12) and others that human gall stones placed in the gall bladders of dogs tend to dissolve spontaneously over a varying period of time.

ANTIQUITY

In attempting to trace back the antiquity of gall stones into prehistoric times which preceded all known written records, certain difficulties are immediately encountered by the paleopathologist. Certain pathologic states have left their unmistakable record in the bones of animals that lived thousands or even millions of years ago such as arthritis, exostoses, fractures, etc. These can be read and studied just as accurately as though the animals were extant instead of extinct. However lesions involving the soft tissues have long disintegrated leaving only the force of logic of comparison, deduction and conclusion to form a working hypothesis.

Since it is known that bacteria play such an important role in the causation of the inflammatory process which initiates the mechanism of gall stones, it becomes necessary to trace their occurrence back to the early times of prehistoric mammals. As for the changes taking place in the gall bladder there is no reason to believe that the basic nature of the biologic processes have changed considerably or suddenly throughout the ages.

It is sometimes assumed that bacteria being such simple little things are fairly recent arrivals on this earth. As a matter of fact the contrary is true. Studies

in fossil remains prove conclusively that bacteria are one of the oldest forms of living matter on this earth, if not the oldest.

Bacteria are simple in one respect only. They are simple in morphology. But in their biologic function they manifest an array of biochemical functions that is comparable to the higher forms of life. They are capable of irritation, receptivity, conductivity, responsiveness, growth, reproduction and death. Bacteria as far as we know are the only form of life that can exist on an otherwise lifeless earth.

Bacteria can and do exist without the help of man, but man as well as other mammals cannot live without the help of bacteria. Bacteria alone of all forms of life are capable of taking the inert nitrogen from the free ammonia of the air and synthesizing it into protoplasm (Osborn (22)). Its waste products are the nitrates which are utilized by plants for the synthesis of their protoplasm which in turn forms the basis for the protoplasm of animal life. These primitive bacterial feeders are called *Nitrosomonas*. They were described by Heraeus and Huppe in 1887. According to Osborn they were the first to observe the nitrifiers in action in soil and to prove that they were able to exist with nothing more than ammonia and carbon dioxide as their source of energy. Life today could not exist without these primitive feeders, since they initiate the nitrogen cycle which we require in a more highly developed form of amino acids derived from plant and animal life.

Simple as these bacteria are, they nevertheless have left their fossil remains embedded in lime stone deposits exactly as plants, leaves and other tissues have been recorded. By their fossil remains the antiquity of bacteria have been placed into the Archzeozoic age by Moodie (24). In this country Walcott (25, 26) has succeeded in establishing the presence of bacteria in the pre-Cambrian era thus definitely establishing their age at more than 30,000,000 years.

It is purely speculative, but it is reasonable to assume that the earliest animals had cholecytic disease and probably gall stones.

HEREDITY

No one has come out to declare that heredity operates in the causation of gall stones, yet we have seen the science of genetics grow from an amorphous nebula to a sprouting science. Certain facts commend themselves to our attention. The first of these is the unshakable logic of the inheritance factor of the pigment stones which occur in hemolytic jaundice.

Hemolytic jaundice.—Hemolytic jaundice is an inherited disease. Snyder (27) states that it is the result of a dominant factor with complete penetrance but variable expressivity. In hemolytic jaundice pigment gall stones occur. In fact Pemberton (28, 29) states that in his series of 180 patients 71.7 percent had cholecytic disease and of these 45.6 percent had gall stones. These gall stones are part of the picture of an inherited disease.

To be sure there may be other factors operating in their causation, but Snyder points out that we must not

make the mistake of assuming that because a causative factor may be known, heredity can play no part in its manifestation.

Recently it has been shown that there may exist a strong inheritarice factor even in the case of bacterial disease. Thus in tuberculosis, inheritance is important in determining the degree of susceptibility to the bacterial infection. A recent editorial (30) in the American Medical Association states that although exposure to infection is an important factor in the etiology of tuberculosis, variability in individual susceptibility may be a function of the genetic constitution. This is supported by the work of Lurie (31) who showed in rabbits that he was able to develop three distinct family strains with reference to the susceptibility; namely a highly resistant family, a moderately resistant family and a nonresistant family.

In the case of the formation of gall stones in hemolytic jaundice, there can be no question of the role of the inheritance factors.

Other clinical observations.—From time to time we have observed families in whom there was a high incidence of gall stones. There can be no doubt as to the occurrence of the stones which were recovered by cholecystectomy. However whether these families have a definite trend or whether they merely happen to be instances of coincidence is a problem that we will not attempt to answer at this time; since this is a matter of investigation by students of genetics.

Case 1. Miss McC a spinster of 40 years had epigastric fullness after meals, bloating, belching, intolerance for fried foods, greasy foods, cabbage, onions and cauliflower. An x-ray examination showed the presence of multiple gall stones which were removed at operation (see photograph). In her case there had been no pregnancies to act as an etiologic factor; likewise her older sister also a spinster had a gall bladder full of stones removed. Their mother and maternal grandmother likewise had had their gall bladders removed for stones.

Case 2. Mr. D. R. a government engineer, age 46 years complained of distress after eating, flatulence and intolerance for certain foods. One night he had an attack of excruciating pain in the region of the left costal margin, the pain radiated to the right shoulder blade. Morphine relieved him. An x-ray showed stones in the gall bladder. His father also had trouble with his gall bladder with its ultimate removal when it was found to contain stones.

Case 3. Mr. H. Y. age 42 complained of belching after meals, fullness after meals and attacks of distress under the right costal margin. Occasionally he would have attacks of rather severe pain in the epigastrium which radiated to the back and requiring morphine for relief. An x-ray showed the presence of gall stones which were removed at operation. His mother had also had her gall bladder removed for stones.

These families are representative of dozens of other instances in which there was a high incidence of gall stones in families; and they serve to focus our attention

on the problem whether some families do manifest a special trend in this direction, or whether these are merely instances of coincidence. This problem however will be left to students of genetics to ponder over.

SUMMARY

1. Biliary colic may occur in patients subsequent to the removal of gall stones.
2. Removal of the gall bladder does not eradicate the mechanism of gall stone formation.
3. The mechanism of gall stone formation is not a simple devise; rather it is a complicated biochemical mechanism in which three processes operate; namely, (a) infection, (b) changes in the composition of the bile, (c) biliary stasis.
4. Inflammation of the gall bladder plays a double role. First it causes an increased secretion of the inflammatory exudate into the bile altering its chemical balance and second the inflamed wall loses some of its absorbing power. Both of these processes favor the precipitation of solids from the bile.
5. Stasis of the bile is a common occurrence in numerous functional disorders and does not require a gross abnormality to produce it. It occurs in such minor functional disturbances as sedentary habits, obesity, debilitating states, heart disease, pregnancy, pressure from contiguous organs, etc., as well as from inflamed gall bladders.
6. The formation of gall stones begins with a nidus provided by the inflammatory process which is usually bacterial in origin. About the nidus is precipitated cholesterol, calcium and bile pigments whenever the mechanism which holds these in suspension is disturbed. There exists a definite ratio between the solubility of cholesterol and the bile salts which determines its solubility. This ratio is one part of cholesterol to 20 to 30 parts of bile salts. Whenever the ratio falls to one part of cholesterol to 13 or less parts of bile salts, then cholesterol is precipitated and gall stones are formed. A somewhat similar mechanism controls the solubility and precipitation of calcium and bile pigments.
7. Cholecystectomy does not eradicate the mechanism of gall stone formation which is independent of the anatomic gall bladder.
8. The occurrence of gall stones in the human race is universal. Women have a higher incidence and at an earlier age group than men. Pregnancy is considered an important predisposing factor.
9. Gall stones occur in some animals spontaneously as in cattle, hogs and dogs. In cattle, pregnancy is an important predisposing cause, while middle life and old age are the favorable age groups.
10. Human gall stones when placed experimentally in the gall bladders of dogs disappear spontaneously over a varying period of time.
11. There is no reason to believe that cholelithic disease including gall stones is a recent development in the evolutionary cycle; on the contrary all the signs point to its existence for a long time even before the advent of man.

12. Heredity operates in the production of the pigment gall stones of hemolytic jaundice.
13. Some families manifest a high incidence of gall stones.

REFERENCES:

1. Gaither, E., In Portis Diseases of the Digestive System, Lea and Febiger, Phila., 1941.
2. Lichtman, S. S., Diseases of the Liver, Gall Bladder and Bile Ducts, Lea and Febiger, Phila., 1942.
3. Karsner, H. T., Human Pathology, J. B. Lippincott, Phila., 1942.
4. Walters, W. and Snell, A. M., Disorders of the Gall Bladder and Bile Ducts, W. B. Saunders, Phila., 1940.
5. Rosenow, E. C., The Etiology of Cholecystitis and Gall Stones, *Jour. Inf. Dis.*, 1916, 19, 527.
6. Blalock, A., A Statistical Study of 888 Cases of Biliary Tract Disease, Johns Hopkins Hosp. Bull., 1924, 35, 391.
7. Hanssen, E. C., and Yurevich, A., Bacteriologic Observations in Disease of the Biliary Tract, *Amer. Jour. Dig. Dis.*, 1935, 2, 460.
8. Twiss, J. R., Carter, R. F., and Hotz, R., Determination of Biliary Tract Infection with Encapsulated Duodenal Tube, *Ann. Int. Med.*, 1940, 13, 2104.
9. Best, C. H. and Taylor N. B., The Physiological Basis of Medical Practice, Williams and Wilkins Company, Baltimore, 1943.
10. Andrews, E., Schoenheimer, R., and Hrdina, L., Etiology of Gall Stones, *Arch. Surg.*, 1932, 25, 796.
11. Andrews, E., Hrdina, L., and Dostal, L. E., Etiology of Gall Stones, *Arch. Surg.*, 1932, 25, 1081.
12. Dokart, R. R., Jones, K. K., and Brown, C. F. G., Chemical Factors Concerned in Formation of Gall Stones, *Arch. Int. Med.*, 1938, 62, 619.
13. Walsh, E. L. and Ivy, A. C., Observations of the Etiology of Gall Stones, *Ann. Int. Med.*, 1930, 4, 134.
14. Exner, A., and Heyrovsky, H., Zur Pathogenese Der Cholelithiasis, *Arch. f. klin. Chir.*, 1903, 88, 609.
15. Robertson, H. E., Douchat, G., Pregnancy and Gall Stones, *Surg., Gyn., Obs.*, 1944, 78, 193.
16. Ludlow, A. L., Autopsy Incidence of Cholelithiasis, *Amer. Jour. Med. Sc.*, 1937, 193, 481.
17. Alexander of Tralles, cited by Bett, W. R., A Short History of Some Common Diseases, Oxford University Press, London, 1934, p. 55.
18. Gauss, Harry, and Davis, C. L., The Incidence of Gall Stones in Cattle, *Jour. Amer. Vet. Med. Assn.*, 1932, 81, 71.
19. Totten, cited by Feldman, W. H., Adenomacarcinoma in the Gall Bladder of a Cow, *Jour. Cancer Research*, 1929, 12, 188.
20. Schlotthauer, C. F., and Stalker, L. K., Cholelithiasis in Dogs, *Jour. Amer. Vet. Med. Assn.*, 1936, 88, 758.
21. Meyer, K. F., Niclson, N. H., and Feusier, M. K., The Mechanism of Gall Bladder Infection in Laboratory Animals, *Jour. Inf. Dis.*, 1921, 28, 456.
22. Osborn, H. F., The Origin and Evolution of Life, Charles Scribner's Sons, New York, 1917.
23. Heraeus and Huppa, cited by Osborn, p. 82.
24. Moodie, R. L., Paleopathology, University of Illinois Press, Urbana, Illinois, 1923.
25. Walcott, C. D., Annual Report of 1915 of the Smithsonian Institution, Washington, D. C.
26. Walcott, C. D., Discovery of Algonkian Bacteria, *Proc. Nat. Acad. Sc.*, 1915, p. 256.
27. Snyder, L. H., Medical Genetics, Duke University Press, 1941, Durham, N. C.
28. Pemberton, J. de J., Personal Correspondence.
29. Pemberton, J. de J., The Present Status of the Surgery of the Spleen, *Cincinnati Jour. Med.*, 1942, 22, 564.
30. Editorial, *Jour. Amer. Med. Assn.*, 1944, 124, 649.
31. Lurie, M. B., Heredity, Constitution and Tuberculosis, *Amer. Rev. Tuberc. (supp.)* 1941, 44, 1.

Etiology of Peptic Ulcer --- A New Hypothesis

By

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THE object of this communication is to present a new theory on the etiology of peptic ulcer and to cite facts in support thereof. According to this theory, peptic ulcer is due to an excess of the intrinsic factor of Castle. The various known clinical facts which seem to support this theory follow:

In the case of most of the other body hormones or secretions, there exist fairly wide ranges which extend both above the upper limits of accepted normal to give what we call a hyper- zone, and below the lower limits of normal to give a hypo- state which may extend on down to complete absence of secretion. Those individuals in the hyper- and hypo- zones will usually present certain symptoms which eventually become recognized as disease entities. In the case of the intrinsic factor we recognize pernicious anemia as the disease resulting from a hypo-secretion or an absence of secre-

tion. As yet we have recognized no disease syndrome due to an excess of the intrinsic factor. Since this substance is elaborated by the stomach and duodenum, it seems not too visionary to look for this disease in the stomach and duodenum. Ulcer suggests itself since its etiology is still unknown and particularly since the interaction of intrinsic and extrinsic substances is somewhat in the nature of a digestive process.

Pernicious anemia and ulcer never occur together. There have been extremely rare exceptions to this rule reported. One prominent symptom of pernicious anemia is an absence of free HCl while in ulcer we have high acid values. The achlorhydria has nothing to do with pernicious anemia etiologically, although this finding led to a great deal of research in efforts to prove or disprove its etiological significance prior to the introduction of liver in the treatment of pernicious anemia.

and elucidation of the true nature of this disease. Similarly a vast amount of work has been directed toward the etiological relationship of HCl to ulcer; I think we still can say no such definite relationship has been proved. The same can be said about pepsin and rennin. Yet no one can deny the therapeutic value of alkalies in ulcer. Could it not be, however, that intrinsic substance is inactivated by alkalies? We know that anti-anemic substance is so inactivated.

When the true cause of pernicious anemia became known, it seemed superficially logical that one might be able to produce polycythemia by giving an excess of anti-anemic principle. Experiments in this direction, using large doses of liver extract, were unsuccessful in producing the very high counts seen in polycythemia. If one had a marked excess of intrinsic factor one should expect a large production of anti-anemic principle providing sufficient extrinsic substance were provided in the food, and one would physiologically simulate the above experiments. Actually, ulcer patients show a mild degree of polycythemia, providing their red counts are not lowered by bleeding. If intrinsic substance proves to be an enzyme (a still unproven possibility) the above argument would lose much of its force, since enzymes are not used up quantitatively. Actually on more careful reasoning, one should not expect true marked polycythemia to result from an excess of anti-anemic substance since we know such an excess is stored in the normal liver at all times and is mobilized as needed by the bone marrow. There must be some other factor in the body which controls the number of red cells being matured which succeeds in maintaining a normal red count in health, regardless of how great a store of anti-anemic substance there may be stored in the liver.

Although embolism and various other hypotheses have been advanced at various times to explain the

mechanism of ulcer production, the trend of opinion today is that the disease is a penetrative process depending on gastric contents. Palmer(1) states, "The pathological, clinical and experimental evidence are in accord in indicating that peptic ulcer is a penetrative process beginning in the mucosa and dependent upon the destructive action of acid gastric juice. The explanation of the failure of the mucosa to withstand the acid attack is not clear. Decreased secretion of mucus and excessive continued secretion of acid, have been suggested." Why could not the explanation be the presence of an excessive amount of intrinsic substance in the acid gastric juice which is known to have some digestive-like properties?

Ulcer occurs only in the presence of gastric secretion—the lower end of the esophagus, the stomach, the duodenum, Meckel's diverticulum, etc. This again is a powerful indication that something in the gastric juice is causative.

The secretion of intrinsic substance probably is under the control of the autonomic nervous system as is the secretion of hydrochloric acid. Hence, the widely held clinical belief that the incidence of ulcer is greater during emotional stress as well as the associated high acid values is consistent with this theory. Also the action of enterogastrone and urogastrone in reducing gastric secretion is consistent with the theory, since they are thought to exert their influence by way of the autonomies.

Experimental approaches toward the testing of this theory are most difficult due to the lack, as yet, of isolation of the intrinsic factor or an exact knowledge of its structure.

REFERENCE

1. Palmer, Walter J., Text-Book of Medicine, Cecil, 99, 1942, 767.

Changes in the Volumes of Blood and Extra-Cellular Fluid in Bowel Obstruction of the Rabbit

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STUDIES of this condition in the rabbit have been of particular interest because of its inability to vomit. Furthermore, gastric and intestinal walls are much thinner than those in the dog, more closely resembling those of man in this respect. Bunting and Jones (1) found that obstruction in this animal produced by ligature of the duodenum was more quickly fatal than obstruction of the pylorus or ileum. This difference they attributed to the glands of Brunner,

which they considered responsible for a toxic secretion. At least one of the present views would be that these glands are simply increasing the loss of electrolyte and water from the blood plasma.

Gamble and McIver (2) found that as the result of pyloric obstruction in the rabbit large quantities of water, fixed base and chloride ion entered the stomach. Furthermore, the skin and muscles lost water and chloride to the blood stream. In spite of this replacement the continued loss to the gastric contents resulted in a considerable reduction in plasma base, a much larger reduction in chlorine and a large increase in an

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undetermined acid factor. Raine and Perry (3) found a reduction in blood chlorides and elevation of non-protein nitrogen in obstruction of small intestine in the rabbit. Recovery was more rapid if the animal were permitted to reabsorb the contents of the obstructed bowel than when such contents were removed. Increasing the intra-intestinal pressure in the obstructed bowel shortened the life of the rabbits, because in their opinion, it stimulated secretion and diminished reabsorption.

There is considerable evidence that a significant decrease in plasma volume occurs in bowel obstruction. Herrin and Meek (4) found in dogs with complete surgical obstruction of the upper jejunum that a marked increase in hemoglobin concentration and red blood cell count occurred. Furthermore, using the brilliant vital red dye, they found a marked reduction in plasma volume. They also found that distending intestinal fistula in dogs resulted in a picture very closely resembling intestinal obstruction. In these animals as well, they demonstrated that intestinal distention resulted in a marked reduction of plasma volume. Aird (5), using vital red, found in both high and low small intestine obstruction in dogs, that the plasma volume was reduced 31 to 50 percent below the normal. Gendel and Fine (6) reported the effect of acute intestinal obstruction in dogs upon their blood and plasma volume. The dogs were anesthetized with nembutal, a ligature placed around the pylorus, the terminal ileum divided and a cannula tied into the upper end. The cannula was then either clamped off or connected to a pressure bottle and the entire small intestine distended with pressure of 15, 20 or 30 cm. of water. The group with the cannula clamped off died in 31 to 34 hours and the average survival time of the second group was 20.8 hours. They concluded that distention of the obstructed intestine in dogs caused an early and progressive loss of blood plasma. The average loss of plasma reached 36.4 percent within 4 to 6 hours and 55 percent within 24 hours. Furthermore, they concluded, distention per se did not cause a loss of fluids into the intestinal lumen, bowel wall or peritoneal cavity. Fine, Hurwitz and Marks (7) found also in clinical patients with distention of the small intestine, whether of functional or mechanical origin that there was a considerable loss in plasma volume. In a patient with a marked obstructive distention of the colon no loss of plasma occurred. This in their opinion ruled out the mechanical effect of a distended viscous upon venous return through the abdomen as a factor causing the reduction in plasma volume. Abbott, Mellors and Muntwyler (8) determined the changes in hematocrit, plasma protein, plasma volume and the volume of extra-cellular fluid in dogs during obstruction of the pylorus, or jejunum, or ileum or colon. There occurred a marked decrease in the volume of plasma and extra-cellular fluid. The concentration of plasma protein always increased except in cases of colonic obstruction. In the latter type, the authors suggested malnutrition as a cause for the lowering of plasma protein. Crandall and Anderson (9) had previously demonstrated in dogs with high intes-

tinal obstruction that there occurred a marked reduction in the volume of extra-cellular fluid.

This paper is concerned with the changes in hematocrit and the volumes of blood and extra-cellular fluid in rabbits during bowel obstruction.

METHODS

The rabbits were anesthetized with ether and the bowel was aseptically obstructed about 15 cm. from the pylorus by a ligature of soft twine. This procedure required less than 20 minutes. The hematocrit was determined with Van Allen tubes and 1.3 percent sodium oxalate solution. The plasma volume was determined with the dye T-1824 (10). The extra-cellular fluid was determined as the volume available to dissolve a known amount of NaCNS (9). The blood for the sulfocyanate determination was drawn 30 to 40 minutes after injection since the values changed slowly at this time and no sulfocyanate was found in the contents of the obstructed bowel. These two determinations were made with the Evelyn colorimeter and two determinations of the normal values were made on separate days. The volume of fluid in the obstructed bowel was determined as the supernatant fluid after centrifugation. This volume in the normal rabbit was found not to exceed 30 cc. Autopsies were done on all animals and no peritonitis or gangrenous bowel was found.

RESULTS

The data are presented in Table 1. In 5 of the 7 rabbits the percent increase in hematocrit was 23 percent or more. In Rabbits 3 and 5 it was only 5 and 10 percent respectively but in both of these animals the volume of blood cells decreased 19 and 13 cc. respectively. Hemolysis was not detected in the serum but the difference seems more likely due to loss of cells from the circulation than to technical error. The decrease in plasma volume ranged from 23 to 29 per cent. The volume of extra-cellular fluid after deduction of the plasma volume decreased, with one exception, 19 to 34 percent. In one rabbit the decrease in extra-cellular fluid was due to shrinkage in plasma volume. Near the end, the rabbits showed cyanosis of the tongue and in the white rabbits particularly of the lips. The ears were blanched and cold. Rubbing the ears resulted in very little hyperemia and then it was transitory. Application of xylene to the ears elicited slight hyperemia of very short duration. In spite of all this evidence of circulatory failure, a rabbit would maintain a fairly normal posture. However, when 3 or 4 cc. of blood were slowly drawn by heart puncture, unconsciousness intervened and the end began. A similar bleeding of 15 to 25 cc. in a normal rabbit caused no bad effects.

In bowel obstruction conditions are changing markedly so that at the termination the picture presents a number of deviations from the normal and the question arises as to the relative importance of these in the pathogenesis of obstruction. The data of this study emphasize the circulatory failure. However, the stomach and duodenum are greatly distended with fluid, which being almost neutral in reaction favors

bacterial activity. The distention might interfere with the blood supply to the bowel and the distended viscus might interfere with respiratory movement and venous return through the portal vein and vena cava. Raine and Perry (3) found that increasing the distention, shortened the life. On the other hand, the data of Rabbit 8 seem to indicate that these factors are of less importance than the circulatory changes. Over 22 percent of its extra-cellular fluid was excreted in the urine following the intravenous injection of sucrose. When obstruction resulted in a further 14 percent reduction in extra-cellular fluid, the failure occurred. The latter reduction approximated the fluid volume of obstructed contents. In this case, the distention was less and yet the length of life was decidedly less than the animal's weight would lead one to expect but did occur when the

the plasma and with the exception of Rabbit 3 from the tissue fluid, outside the blood circulation. The movement of fluid from tissue spaces to dilute the hemoconcentration, is illustrated by the data of Rabbit 6. Bowel obstruction has been considered as a type of shock (11) but in the former, fluid leaves the tissue spaces as well as the blood stream. Actually the end result may be the same but theoretically it would seem that a reduction in volume of tissue fluid would place a greater handicap on the transference of materials between the blood and the tissues than would a loss of fluid into the tissue spaces.

The physiological effect of a loss of fluid into the bowel contents is a reduction of plasma volume with its attendant hemoconcentration and circulatory insufficiency as shown by the cyanosis and the poor hyperemic

TABLE I

Decrease in the Volume of Blood and Extra-Cellular Fluid during Bowel Obstruction in the Rabbit

Rabbit	Condition	Hematocrit	Plasma Volume	Blood Volume Quantity	Percent of Body Wt.	Volume of Extra-cellular Fluid Minus Plasma Volume	Fluid Contents of Ob- structed Bowel	Length of Life
			c.c.			c.c.	c.c.	hours
(1)	Normal	33.5	121.7	183	6.7	952		
	Obstructed	41.5	71.5	122		691		18
(2)	Normal	31.5	166.0	242	7.7	1014		
	Obstructed	40.0	104.0	173		661	260	23.5
(3)	Normal	29.5	121.7	173	7.3	562		
	Obstructed	31.0	72.0	104		557	188	17
(4)	Normal	34.5	175.0	271	5.9	923		
	Obstructed	48.5	106.0	207		743	310	16
(5)	Normal	24.0	109.2	144	7.9	497		
	Obstructed	26.5	69.1	92		351	118	11.5
(6)	Normal	32.5	173.4	257	6.5	1177		
	Obstructed (14 hrs.)	45.5	96.7	177		803		
	Obstructed (17½ hrs.)	40.0	113.4	189		770	269	18.66
(7)	Normal	24.2	117.0	154	7.6	486		
	Obstructed	41.5	Lost prior to more study				232	12
(8)	Normal	36.5	150.8	237	6.5	1037*		
	Dehydration after an injection of sucrose					805*		
	Obstruction					654*	157	12

* Total extra-cellular fluid volume

loss of extra-cellular fluid approximated that for example of Rabbits 5 or 6.

COMMENT

Obstruction of the jejunum in the rabbit results in a marked increase in the fluid content of the bowel contents. The movement of fluid into the lumen of the obstructed bowel may be in part due to the spontaneous secretion shown by the digestive glands to secretagogues in the food since the rabbits were not in the post-absorptive state and to the distention caused by the accumulation of contents. Herrin and Meek (4) have demonstrated that distention of intestinal fistula in dogs greatly stimulates the distended bowel to secrete and this effect may operate in the rabbit as well. The data of this study, show that the fluid has been drawn from

response to mechanical or chemical cutaneous stimuli to the ears. We were much impressed by the low circulatory reserve of these animals. The withdrawal of a few cubic centimeters of blood from the obstructed rabbit, which had not seemed to be in such a poor condition brought on the fatal termination. Anoxemia of the anoxic type has been found to occur in dogs with bowel obstruction (12) or that have lost intestinal fluid by a distended intestinal fistula (13).

The question has been raised as to the vital significance of the loss of chlorine, in bowel obstruction (14). Dragstedt and Ellis (15) allowed dogs to lose gastric juice through gastric fistula to the point where the blood chlorides were lower than occurred with bowel obstruction and the dogs lived, although in a weakened condition. Taylor, Weld and Harrison (16)

produced a similar picture by causing normal dogs to lose gastric juice by vomiting. The dogs of both groups of workers had a great increase in plasma CO₂, indicating that the loss of Na was not as great as chlorine. Dragstedt's dogs apparently did not have a material reduction in plasma volume since the hematocrit, red cell count and hemoglobin values did not increase. On the other hand, Gamble and associates found in both dog (17) and rabbit (2) with pyloric obstruction that a large amount of Na appeared in the gastric contents and the serum Na was reduced. In the dogs with pyloric obstruction Gamble and Ross found a marked increase in the concentration of the serum proteins indicating a reduction in plasma volume. Gamble pointed out that loss of Na is accompanied by dehydration whereas, the loss of chlorine can be compensated to some extent by retention of the bicarbonate ion. It seems likely therefore, that the striking difference between a simple loss of gastric juice and pyloric obstruction, is the loss of Na and the accompanying dehydration and circulatory failure in the latter condition. Furthermore, in obstruction there is present the factor of distention which might stimulate other secretory portions of the stomach than the fundic glands and in this way cause a loss of sodium. The evidence therefore points to the conclusion that of the loss of electrolytes, the loss of Na is the more important since it leads to a reduction in the volume of circulating plasma and tissue fluid. Insufficiency of the circu-

lation results with its accompanying tissue anoxia and when this failure is great enough, the fatal termination occurs.

SUMMARY

Experimental obstruction of the upper portion of the jejunum by a soft ligature in rabbits resulted in an increase in the blood hematocrit of 23 to 40 per cent in 6 of 8 animals. The increase in the other two was 5 and 10 per cent but their total volume of red cells decreased. There was no visible sign of hemolysis in the serum of any of the rabbits.

The plasma volume decreased in all animals, the percentage decrease ranging from 23 to 29 per cent.

The volume of extra-cellular fluid outside of the circulating blood stream decreased, with one exception, 19 to 34 per cent below the normal. The data of one animal clearly showed the movement of tissue fluid into the blood stream after some hemoconcentration had been attained. In Rabbit 3, tissue fluid apparently did not significantly move into the blood stream.

Other evidence of circulatory failure, was the apparent cyanosis, blanched, cold skin of the ear, poor cutaneous, hyperemic response to stimuli and inability to withstand removal of a small volume of blood.

It is concluded that the loss of sodium, chloride and water into the obstructed bowel of rabbits leads to a reduction of plasma and tissue fluid volumes, with the accompanying circulatory failure.

REFERENCES

- Bunting, C. H. and Jones, A. P. Intestinal obstruction in the rabbit. *J. Exper. Med.* 17, 192 (1913) and 18, 25, (1913).
- Gamble, J. L. and McIver, M. A. A study of the effects of pyloric obstruction in rabbits. *J. Clin. Invest.* 1, 531 (1925).
- Raine, F. and Perry, M. C. Intestinal obstruction. *Arch. Surg.* 19, 478 (1929).
- Herrin, R. C. and Meek, W. J. Distention as a factor in intestinal obstruction. *Arch. Int. Med.* 51, 152 (1933).
- Aird, I. The behavior of the blood volume in intestinal obstruction and strangulation. *Brit. J. Surg.* 26, 418 (1938).
- Gendel, S. and Fine, J. The effect of acute intestinal obstruction on the blood and plasma volumes. *Ann. Surg.* 110, 25 (1939).
- Fine, J., Hurwitz, A. and Marks, J. A clinical study of the plasma volume in acute intestinal obstruction. *Ann. Surg.* 112, 546 (1940).
- Abbott, W. E., Mellors, R. C. and Munizwyler, E. Fluid, protein and electrolyte alterations in experimental intestinal obstruction. *Ann. Surg.* 117, 39 (1943).
- Crandall, L. A. and Anderson, M. X. The estimation of the state of hydration of the body by the amount of water available for the solution of sodium thiocyanate. *Am. J. Dig. Dis. and Nutrition* 1, 126 (1934).
- Gibson, J. G. and Evelyn, K. A. Clinical studies of blood volume. Adaptation of the method to the photoelectric microcolorimeter. *J. Clin. Invest.* 17, 153 (1938).
- Moon, V. H. Shock and Related Capillary Phenomena. Oxford University Press, New York, 1938.
- Haden, R. L. and Orr, T. G. The oxygen content of the venous blood of the dog after upper gastrointestinal tract obstruction. *J. Expt. Med.* 46, 709 (1927).
- Herrin, R. C. Chemical changes in blood and intestinal juice produced by the loss of intestinal juice. *J. Biol. Chem.* 108, 547 (1935).
- Besser, E. L. Causes of death in cases of mechanical intestinal obstruction. *Arch. Surg.* 41, 970 (1940).
- Dragstedt, L. R. and Ellis, J. C. The fatal effect of the total loss of gastric juice. *Am. J. Physiol.* 93, 407 (1930).
- Taylor, N. B., Weld, C. B. and Harrison, G. K. Experimental intestinal obstruction. *Canad. M. A. J.* 29, 236 (1933).
- Gamble, J. L. and Ross, S. G. The factors in the dehydration following pyloric obstruction. *J. Clin. Invest.* 1, 403 (1925).

The Effect of Aluminum Hydroxide Upon Food Utilization in Human Subjects

By

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IT IS well known that aluminum hydroxide is an excellent protein and enzyme adsorbent. In recent years it has also been demonstrated that aluminum hydroxide markedly inhibits gastric digestion. Komarov and Krueger (1) have shown that feeding aluminum hydroxide to dogs inhibits the secretion of gastric juice and also decreases the activity of pepsin. This was observed even in gastric pouches not in direct contact with the agent. Komarov and Komarov (2) have pointed out that aluminum hydroxide, when added to the gastric juice of dogs *in vitro*, quantitatively removes the pepsin from solution. Schiffri and Komarov (3) have shown that the presence of aluminum ions in a solution of the enzyme inhibits proteolytic activity at pH values at which the enzyme is not precipitated. In view of the above facts it seemed of some interest and importance to determine the effect of prolonged administration of aluminum hydroxide to human subjects on the digestion and absorption of foods, since such treatment is common practice in the handling of ulcer cases.

Beazell, Schmidt, and Ivy (4) found that aluminum hydroxide added to pancreatin *in vitro* did not alter the tryptic or lipolytic activity of the preparation. These workers also demonstrated that prolonged administration of aluminum hydroxide to dogs on a standard diet did not alter the fecal fat or nitrogen content. So far as we have been able to determine, the present work represents the first report dealing with the effect of aluminum hydroxide on digestion and absorption in human subjects.

EXPERIMENTAL

A healthy subject with no demonstrable gastro intestinal pathology was selected to serve as a normal control. The subject first collected twenty-four hour urine and feces samples for seven days without previous administration of aluminum hydroxide. This was followed by a period in which 60 cc of amphogel was taken in six divided doses spaced throughout the day. Ordinarily, doses were taken after each meal, midway between meals, and before retiring. A glass of water was taken with each dose. A normal average diet was ingested during both periods.

A hospital patient with a known gastric ulcer was chosen as subject for studying the effect of aluminum hydroxide under therapeutic conditions. The gastric lesion in this subject was shown by x-ray and gas-

troscopy to be located on the lesser curvature about nine centimeters from the pylorus. This subject was put on ulcer management until evidence of healing of the lesion was shown by gastroscopy. At that time a diet of C-180, P-75, F-80, given at 3 feedings, and supplemented by 3 ounces of milk given at hourly intervals from 7:30 A.M. to 7:30 P.M., was started. Vitamin supplements were supplied. This regimen was continued for twelve days to serve as control period, and then 5 cc of amphogel, given hourly from 8:00 A.M. to 8:00 P.M., was added to the control diet. Twenty-four hour

TABLE I
Composition of feces and urine for 24 hour periods

NORMAL SUBJECT *No Aluminum Hydroxide in Diet*

Fecal Fat Grams per 24 hours	Fecal Carbohydrate* Grams per 24 hours	Urine Nitrogen Grams per 24 hours	Fecal Nitrogen Grams per 24 hours	U.N./F.N.
6.00	0.31	14.9	2.24	6.7
4.90	0.46	14.5	1.90	7.6
		14.9	2.70	5.5
Av. 5.45	Av. 0.39	19.2	2.34	8.3
		18.5	2.86	6.5
		17.1	2.24	7.6
		17.1	3.10	5.5
		Av. 16.6	Av. 2.49	Av. 6.6

Aluminum Hydroxide Present in Diet

Fecal Fat Grams per 24 hours	Fecal Carbohydrate* Grams per 24 hours	Urine Nitrogen Grams per 24 hours	Fecal Nitrogen Grams per 24 hours	U.N./F.N.
7.00	0.11	16.3	2.95	5.5
8.24	0.56	13.7	2.38	6.0
9.88	0.20	13.0	2.08	6.3
		15.6	2.02	7.7
Av. 8.36	Av. 0.29	12.2	1.93	6.3
		16.9	2.00	8.5
		Av. 14.6	Av. 2.23	Av. 6.7

*Carbohydrate as glucose.

urine and feces samples were collected for analysis.

Urine samples were collected in bottles containing toluol as preservative. Feces were collected, placed in one-half gallon jars, 1 volume of feces mixed with 3 volumes of water and a sample of 2-3 cc removed for pH determination. 60 cc of concentrated sulfuric acid was stirred into the mixture and after several days, following emulsification, the acidified mixture was diluted to 1000 cc and reserved for analysis. pH determinations on the urine and feces were made with the glass electrode using a Beckman pH meter. Titratable acidity of urine was estimated by titration with .1 N

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sodium hydroxide in the presence of potassium oxalate, using phenolphthalein as an indicator. Nitrogen determinations were done according to the Kjeldahl method. The determination of total carbohydrate in the feces involved hydrolysis with 0.5 N sulfuric acid for 5

TABLE II
Composition of feces and urine for 24 hour periods

GASTRIC ULCER PATIENT
No Aluminum Hydroxide in Diet

Fecal Fat Grams per 24 hours	Fecal Carbohydrate Grams per 24 hours	Urine Nitrogen Grams per 24 hours	Fecal Nitrogen Grams per 24 hours	U.N./F.N.
0.64	0.52	10.2	0.15	65.0
0.34	0.24	10.0	0.44	22.5
0.34	0.28	10.5	0.36	28.7
		10.3	0.52	19.8
Av. 0.44	Av. 0.35	Av. 10.3	Av. 0.37	Av. 34.0

Aluminum Hydroxide Present in Diet

Fecal Fat Grams per 24 hours	Fecal Carbohydrate Grams per 24 hours	Urine Nitrogen Grams per 24 hours	Fecal Nitrogen Grams per 24 hours	U.N./F.N.
0.64	0.41	7.7	0.80	10.0
0.70	0.14	7.4	1.43	5.2
	0.38	6.1	0.20	29.0
Av. 0.67	Av. 0.31	14.0	2.56	5.5
		12.0	0.52	24.0
		Av. 9.50	Av. 1.10	Av. 14.7

TABLE III

Urine Titratable Acidity and Urine and Feces pH for 24 Hour Periods

NORMAL SUBJECT

No Aluminum Hydroxide in Diet

Urine pH	Titratable Acidity cc.O.1N	Feces pH
6.42	205.7	6.15
5.45	479.3	5.90
5.40	470.1	6.10
5.25	505.0	5.90
5.48	456.0	5.90
5.30	545.6	6.00
5.32	459.4	6.00
Av. 5.51	Av. 445.8	Av. 5.99

Aluminum Hydroxide Present in Diet

Urine pH	Titratable Acidity cc.O.1N	Feces pH
5.80	377.2	6.95
5.95	191.9	7.15
6.28	91.0	6.90
5.72	121.5	5.98
5.30	229.3	6.72
5.70	201.0	6.50
5.65	200.0	6.92
5.15	414.2	6.80
5.35	360.4	6.65
5.50	262.8	6.70
6.30	224.4	6.90
5.70	212.0	6.40
6.30	189.0	6.90
5.60	307.0	6.30
Av. 5.72	Av. 241.5	Av. 6.69

hours, precipitation according to the iron method of Steiner, Urban, and West (5), and estimation of fermentable sugar in the filtrates according to the method

of Somogyi (6). Fat content of the feces was estimated according to the method of Saxon (7).

DISCUSSION

In the normal subject, the collection of samples was very carefully done and as can be seen from the tables, remarkably consistent results were obtained. In order to show any change in protein utilization the ratio of nitrogen excreted in the urine to the nitrogen excreted in the feces was calculated. The average values for this ratio were 6.6 and 6.7 in the control and aluminum hydroxide periods respectively, which indicates no interference of aluminum hydroxide with protein utilization in this case.

Accurate daily feces sampling in the study of the hospitalized subject could not be secured because of severe constipation and feces impaction. Nitrogen ratios during the control period averaged 34.0, while the average was 14.7 with aluminum hydroxide. Further-

TABLE IV
Urine Titratable Acidity and Urine and Feces pH for 24 Hour Periods

GASTRIC ULCER PATIENT

No Aluminum Hydroxide in Diet

Urine pH	Titratable Acidity cc.O.1N	Feces pH
5.75	263.8	7.95
6.20	177.5	8.15
5.85	334.3	8.42
5.55	332.9	8.05
6.30	199.5	8.30
6.35	199.8	8.15
5.15	320.0	7.40
Av. 5.88	Av. 263.9	Av. 8.06

Aluminum Hydroxide Present in Diet

Urine pH	Titratable Acidity cc.O.1N	Feces pH
5.72	196.9	7.92
6.35	89.0	8.30
6.55	224.0	8.40
6.85	56.4	8.10
5.60	287.7	7.60
5.30	246.4	8.10
5.60	495.0	8.30
5.12	90.0	7.48
5.80	172.2	7.35
6.45	159.0	7.30
6.10	89.0	7.35
6.10	171.1	7.75
5.92	340.7	7.15
5.70	77.7	7.49
	70.3	7.82
	161.6	7.50
Av. 5.97	Av. 182.9	Av. 7.80

study to confirm this was not done because cooperation in collecting samples could not be obtained.

Fat and carbohydrate determinations on the feces of the normal subject were carried out on the last two days of the control period and on the last three days of the aluminum hydroxide period. The results show that the ingestion of aluminum hydroxide was without appreciable effect upon the utilization of fat and carbohydrate. Similar results were obtained in case of the gastric ulcer patient, who, however, excreted much less

fecal fat than the normal subject, presumably because of the widely different diets of the subjects. Tables I and II summarize the experimental findings.

Aluminum hydroxide apparently caused a small but definite increase in urinary pH. The normal subject showed an average urine pH of 5.51 for the control period, and 5.72 for the aluminum hydroxide period. The ulcer patient showed values of 5.88 and 5.97 respectively. A much more marked effect of aluminum hydroxide upon total titratable urinary acidity was observed in both subjects. The normal subject showed an average 24-hour titratable urine acidity of 445 cc of 0.1 N acid during the control period, which dropped to 241 cc during the aluminum hydroxide period. The corresponding values for the ulcer patient were 265 cc and 183 cc respectively. The decrease in urinary acidity under the influence of aluminum hydroxide ingestion was probably due to a decrease in the excretion of urinary phosphate. Fauley, Freeman, Ivy, et al (8) have shown that urinary phosphate excretion in humans on light ulcer diets was decreased about 60 percent when aluminum hydroxide was given orally. On the other hand, fecal phosphate excretion greatly increased as the

result of the formation of insoluble aluminum phosphate. Evidence was presented that much of this fecal phosphate had been removed from the body, leading to a phosphate deficiency. According to these facts we believe that the removal of phosphate ions from the blood by aluminum hydroxide therapy should be reflected in a somewhat higher urine pH and a lowered titratable acidity. Our findings on humans agree with this interpretation.

The average fecal pH value of the normal subject for the control and aluminum hydroxide periods were 5.99 and 6.69 respectively, while the values for the ulcer patient were 8.06 and 7.8. Tables III-IV give the experimental result on acidity of urine and feces.

Summary: Administration of aluminum hydroxide to a normal subject did not interfere with the utilization of carbohydrate, fats, or proteins of the diet. Apparently there was no interference with carbohydrate and fat utilization in a gastric ulcer subject, but results on protein utilization were inconclusive.

Aluminum hydroxide administration caused slight increases in urinary pH and very definite decreases in total urinary acidity.

REFERENCES

1. Komarov, S. A. and Krueger, Luise. The Effect of Aluminum Hydroxide Gel on Gastric Secretion in the Dog. *Am. J. Dig. Dis.*, 7:170, 1940.
2. Komarov, S. A. and Komarov, Olga. The Precipitability of Pepsin by Colloidal Aluminum Hydroxide. *Am. J. Dig. Dis.*, 7:166, 1940.
3. Schiffarin, M. J. and Komarov, S. A. The Inactivation of Pepsin by Compounds of Aluminum and Magnesium. *Am. J. Dig. Dis.*, 8:215, 1941.
4. Beazell, J. M., Schmidt, C. R. and Ivy, A. C. The Effect of Aluminum Hydroxide Cream on Absorption from the Gastrointestinal Tract. *Am. J. Dig. Dis.*, 5:164, 1939.
5. Steiner, A., Urban, F. and West, E. S. Iron and Thorium Precipitation of Biological Fluids for Sugar and other Analyses. *J. Biol. Chem.*, 98:289, 1932.
6. Shaffer, P. A. and Somogyi, M. Copper-iodometric Reagents for Sugar Determination. *J. Biol. Chem.*, 100:695, 1933.
7. Saxon, Gordon J. A Method for the Determination of the Total Fats of Undried Feces and Other Moist Masses. *J. Biol. Chem.*, 17:99, 1914.
8. Fauley, G. B., Freeman, S., Ivy, A. C., Atkinson, A. J. and Wigodsky, H. S. Aluminum Phosphate in the Therapy of Peptic Ulcer. *Arch. Int. Med.*, 67:563, 1941.

Some Effects of Magnesium Trisilicate Ingestion Upon Blood, Urine, and Feces of Human Subjects

By

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MUTCH (1) introduced the use of magnesium trisilicate as an antacid for the treatment of peptic ulcer in 1936. He demonstrated that the compound is effective in neutralizing hydrochloric acid and is also a powerful adsorbing agent for various dyes, alkaloids, bacterial toxins, and putrefactive amines. While it is generally understood that most of orally ingested magnesium trisilicate is excreted in the feces, little has been

reported relative to the detailed effects of such ingestion upon blood and urine. Page, Heffner, and Frey (2), studied the excretion of silica in the urine of humans while taking 5 grams of hydrated magnesium trisilicate daily. They found approximately 5 percent of the silica contained in the trisilicate to be excreted in the urine.

The present paper reports observations on the effects of magnesium trisilicate ingestion upon blood and urine magnesium and calcium values, urine and feces pH, titratable acidity, and the utilization of carbohydrates, fats, and proteins in human subjects.

*From the Department of Biochemistry, University of Oregon Medical School, Portland, Oregon. Taken from a thesis presented by Cleota Pennoyer for the degree of Master of Science in Biochemistry.

Submitted Sept. 5, 1944.

OUTLINE OF STUDY

Observations were made upon ten subjects. These included seven healthy students and professors, and three cases of diagnosed peptic ulcer. In general a control period of four to seven days was run on each subject and this was followed by a similar period during which 6 grams of Mallinckrodt's magnesium trisilicate were ingested in three doses of 2 grams each. The trisilicate was taken midway between meals and before retiring. Ordinary normal diets were eaten by the healthy subjects, and restricted diets by the ulcer patients. Except as indicated, blood for magnesium and calcium determinations was drawn from the subjects before breakfast. Twenty-four hour urine samples were collected and preserved with toluene. Twenty-four hour feces samples were collected in fruit jars and mixed with two to four volumes of water. A few cc. were taken for pH

sampling. 1 cc. of the acidified filtered urine was taken for analysis. Urine magnesium was determined on 5 cc. of supernatant fluid after calcium precipitation by the modified Denis procedure. Urine acidity was determined by titration with 0.1 N sodium hydroxide after addition of potassium oxalate. All pH measurements were made with the glass electrode, using the Beckman pH meter. Nitrogen of feces and urine was determined by the Kjeldahl method. Saxon's method (5) was used for the estimation of total fat in feces. Fermentable sugar of feces was determined on samples hydrolyzed by boiling 5 hours with 0.5 N sulfuric acid. The hydrolysate was precipitated by the iron method of Steiner, Urban, and West (6), and fermentable sugar estimated according to the procedure of Somogyi (7), using Shaffer - Hartmann - Somogyi reagent number 50 (8).

TABLE I

The Effect of Daily Ingestion of 6 Grams of Magnesium Trisilicate Upon Serum and Urinary Calcium and Magnesium.

(Values are Averages for Periods.)

Subject	Days	Serum Calcium mg./100 cc.	Urine Calcium mg. 24 hrs.	Serum Mag. mg./100 cc.	Urine Mag. mg. 24 hrs.
CONTROL PERIOD					
K.R.	7	10.1	253	2.1	104
B.D.	6	11.2	218	1.9	71
R.R.	6	11.0	249	2.1	94
C.W.	7	10.3	399	2.0	114
E.W.	7	11.0	353	2.2	99
W.T.	6	10.8	168	2.2	69
P.S.*	5	10.7	446	1.9	127
E.K.*	3				
Average		10.7	298	2.07	97
MEDICATION PERIOD					
K.R.	4	10.4	329	2.5	163
B.D.	5	10.1	248	1.9	174
R.R.	5	10.6	228	1.9	126
C.W.	5	9.9	348	2.1	99
E.W.	5	10.4	321	2.8	164
W.T.	4	10.5	225	2.3	139
P.S.*	4	11.0	376	2.1	201
E.K.*	2				
Average		10.4	296	2.26	152

*Peptic ulcer cases on diet.

measurement and sufficient sulfuric acid added to the remainder to make the acid content ten percent after dilution to volume (1000 cc.). The samples were permitted to stand several days, with occasional shaking, before analysis. This was necessary to promote emulsification for uniform sampling.

Serum calcium was determined by the Clark-Collip modification of the Kramer-Tisdall method (3) and serum magnesium by the Denis method (4) modified by the use of 1 gram Amidol (2, 4-diaminophenol dihydrochloride) in 100 cc. of 20 percent sodium bisulfite as reducing agent (9). Urine calcium was determined by the method for blood. Care was taken to acidify the twenty-four hour sample with hydrochloric acid before

TABLE II

Rate of Absorption of Magnesium Trisilicate

A. 6 Grams Magnesium Trisilicate taken at 8:10 A.M., Subject E. W.

Time	Serum Calcium mg. per 100 cc.	Serum Magnesium mg. per 100 cc.
8:00 A.M.	10.04	1.67
8:40 A.M.	10.04	1.75
9:10 A.M.	10.04	2.30
9:40 A.M.	10.23	2.30
10:10 A.M.	10.04	2.43
11:00 A.M.	10.42	2.43
12:00 A.M.	10.23	2.52
2:00 P.M.	10.42	3.63
4:00 P.M.	10.42	2.43
8:00 A.M.	10.34	2.55

B. 6 Grams Magnesium Trisilicate taken at 8:10 A.M., 75cc. of 0.1N Hydrochloric Acid taken in 25cc. doses at 8:10, 9:10, and 10:10 A.M., Subject E.W.

8/12/41 9:10 A.M.	10.34	2.46
10:10 A.M.	10.34	2.46
12:00 A.M.	10.42	2.80
2:00 P.M.	10.42	4.87
4:00 P.M.	10.43	2.09
8/13/41 8:00 A.M.	10.42	2.62

A summary of the findings are recorded in Tables I-IV.

DISCUSSION

The ingestion of magnesium trisilicate caused no significant change in serum calcium (Table I). In some individuals there was a small increase and in others a small decrease, the over all average amounting to a decrease of about 3 percent. No significant change in urinary calcium excretion was demonstrated during the test periods.

Serum magnesium concentrations showed a definite increase when magnesium trisilicate was taken, the average increase being about 9 percent. Some individuals however, showed marked elevation of serum magnesium with resultant drowsiness. This was especially true in the case of E. W. whose average serum magnesium was elevated 27 percent during the trisilicate period. This individual variation is probably related

to variations in gastro-intestinal acidity. The ingestion of hydrochloric acid during the trisilicate period markedly increased serum magnesium levels. Judging on the basis of serum magnesium concentrations maximum absorption of trisilicate after a 6 gram dose occurred in 5-6 hours regardless of gastro-intestinal acidity (Table II). It is of interest to note that the serum magnesium of an individual was generally highest during the first part of a trisilicate period and fell toward normal during the period. The most reasonable explanation of this phenomenon seems to be that the gastro-intestinal acidity was highest at the beginning of the period and decreased with trisilicate administration due to the acid neutralizing action of the compound.

TABLE III

The Effect of Daily Ingestion of 6 Grams of Magnesium Trisilicate Upon Urinary and Feces pH and Urinary Titratable Acidity.
(Values are average for Periods)

Subject	Days	Urine pH	Urine Acidity cc. O. IN	Feces pH
R.R.	6	5.96	333	
C.W.	7	5.86	427	
C.P.	9	5.83	223	6.14
E.W.	8	5.44	568	6.36
P.S.*	5		543	
E.K.*	21	6.17	360	8.05
Average		5.85	409	6.85
MEDICATION PERIOD				
R.R.	5	6.35	246	
C.W.	5	5.94	366	
C.P.	7	6.41	93	6.47
E.W.	5	6.18	273	6.73
P.S.*	4		407	
E.K.*	10	6.67	241	8.48
Average		6.30	271	7.23

*Peptic ulcer cases on diet.

The urinary excretion of magnesium was increased an average of 56 percent during the trisilicate periods. This represented the magnesium equivalent of about 6.5 percent of the ingested trisilicate. Page, Heffner, and Frey found about 5 percent of the silica equivalent of 5 gram divided doses of trisilicate to be excreted in the urine.

In view of the increased absorption of magnesium from trisilicate as the result of increased gastro-intestinal acidity the absorption of trisilicate as such appears unlikely. Page, Heffner and Frey suggest that gastric hydrochloric acid decomposes trisilicate into soluble magnesium salts and silicic acids, the latter being converted to soluble silicate by alkaline fluids in the intestine. The soluble magnesium salts and silicates are absorbable. It is interesting to note that the silicate and magnesium absorptions from trisilicate are in about the same proportions, 5.2 and 6.5 per cent of the trisilicate contents of magnesium and silica, respectively.

Urinary pH was increased an average of about 8 percent and, correspondingly, the titratable acidity of the urine was decreased an average of about 34 percent during the trisilicate periods. Feces pH was increased an average of 5.5 percent (Table III).

The utilization of carbohydrates and fats was essentially unaffected by trisilicate, though protein absorption was definitely decreased, as shown by an average increase in fecal nitrogen of 110 percent during trisilicate ingestion (Table IV). On the average this increased fecal nitrogen represented a loss of 6.25 grams of protein per day, amounting to 6-10 percent of the protein of the ordinary diet. This loss would be of little consequence in cases with adequate protein intake.

CONCLUSIONS

1. The effect of ingesting 6 grams of hydrated magnesium trisilicate daily for periods of several days upon urine and blood magnesium and calcium, urine pH and,

TABLE IV

The Effect of Daily Ingestion of 6 Grams of Magnesium Trisilicate Upon the Nitrogen of Urine, and Nitrogen, Carbohydrate, and Fat of Feces

(Values given are averages for periods expressed in grams per 24 hours).

Subject	Days	Urinary Nitrogen	Feces Nitrogen	Feces Fat	Feces Carbohydrate
CONTROL PERIOD					
E.W., healthy male instructor	8	16.0	1.15	4.93	0.47
C.P., healthy female student	9	8.7	0.90	3.70	0.57
E.K., diagnosed peptic ulcer	21	15.2	0.71		
Average		13.3	0.92	4.31	0.52
MEDICATION PERIOD					
E.W.	6	20.1	2.19	4.10	0.33
C.P.	7	7.7	2.08	4.46	0.31
E.K.	10	13.1	1.53		
Average		13.6	1.93	4.28	0.32

titratable acidity, feces pH, and the absorption of carbohydrates, fats and proteins in humans has been studied.

2. Serum calcium was slightly decreased, and urinary calcium was unchanged.

3. Serum magnesium levels were generally definitely, and in some cases markedly increased, with resultant drowsiness. Urinary magnesium was increased an average of 56 percent.

4. Urinary pH was increased an average of about 8 percent, and titratable acidity was decreased 34 percent. Feces pH was increased 5.5 percent.

5. The utilization of carbohydrates and fats was essentially unchanged. Protein absorption was decreased and represented the loss of 6-10 percent of dietary protein.

6. An average of about 6.5 percent of the magnesium content of trisilicate ingested was absorbed and excreted in the urine. This was markedly increased by increased acidification of the gastro-intestinal tract.

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REFERENCES

- Mutch, N. Hydrated Magnesium Trisilicate in Peptic Ulceration. *Br. Med. J.* 1:254, 1936.
- Page, R. C., Hefner, R. R., and Frey, A. Urinary Excretion of Silica in Humans Following Oral Administration of Magnesium Trisilicate. *Am. J. Dig. Dis.*, 8:13, 1941.
- Clark, E. P. and Collip, J. B. A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification. *J. Biol. Chem.* 63:461, 1925.
- Denis, W. The Determination of Magnesium in Blood, Plasma, and Serum. *J. Biol. Chem.*, 52:411, 1922.
- Saxon, Gordan J. A Method for the Determination of the Total Fats of Undried Feces and Other Moist Masses. *J. Biol. Chem.*, 17:99, 1914.
- Steiner, A., Urban, E., and West, E. S. Iron and Thorium Precipitation of Biological Fluids for Sugar and Other Analyses. *J. Biol. Chem.*, 98:289, 1932.
- Somogyi, Michael. Reducing Non-Sugars and True Sugar in Human Blood. *J. Biol. Chem.*, 75:33, 1927.
- Shaffer, P. A. and Somogyi, M. Copper-iodometric Reagents for Sugar Determination. *J. Biol. Chem.*, 109:695, 1933.
- Allen, R. J. L. The Estimation of Phosphorus. *Biochem. J.*, 34:858, 1940.

Incidence of Gastritis in Gastric Ulcer

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WE are reporting the gastroscopic findings in fifty-four cases of benign gastric ulcer, primarily because our figures are somewhat at variance with figures previously given in the literature.

Maher, Zinnerger, Schiff, and Shapiro (1) in 14 cases of gastric ulcer found an associated gastritis in 57 percent; the percentage of the various forms is shown in the table below. Templeton and Schindler (2) reported 46 cases of gastric ulcer, with 80 percent showing a gastritis.

However, in another report Schindler and Baxmeier (3) analyzed the gastroscopic picture in 91 cases of gastric ulcer and found only 53 percent with gastritis, the different forms not being specified. They quote Konjetzny and Gutzeit as saying that gastritis is "usually" present, Moutier and Henning that it is "frequently" present.

In our series of 54 patients the ages ranged from 18 to 78 years, the average being 49 years. There were 43 males and 11 females. Seventy-four percent of the ulcers were on the lesser curvature above the angulus, 12 percent in the antrum, 7 percent on the posterior surface, five percent on the anterior surface, and 2 percent on the greater curvature.

The percentage of gastritis in our series, as compared with those quoted above, is as follows:

	Templeton and Schindler
Our Series	Maher et al
Superficial	26 (48%)
Hypertrophic	6 (11%)
Atrophic	7 (13%)
Combined sup. and atrophic 1 (2%)	1 (2%)

The incidence of mucosal hemorrhages and pigment spots in our series was 14 percent.

It will be observed that the chief difference between our results and those previously published is in the incidence of superficial and hypertrophic gastritis. This is probably due to difference in criteria used for interpretation. Most workers are already in essential agreement concerning the total percentage of gastritis found in various groups of cases, but there appears to be some confusion in the differentiation of mild degrees of the hypertrophic and superficial forms. We have always attempted to follow the Schindler (4) classification. When gastrophotography and biopsies come into common use it is to be hoped that closer agreement about the type of gastritis found will be possible.

The amount of gastritis found in the present group of cases is higher than that found in any unselected series, but comparable to the percentage we discovered in patients with duodenal ulcer (5).

SUMMARY

In a series of 54 patients with benign gastric ulcer, an associated gastritis was found in 74 percent.

The most common form of gastritis found was the superficial variety. This is at variance with published reports.

It is to be hoped that the common use of gastrophotography and biopsies will result in closer agreement about the type of gastritis found.

REFERENCES

- Maher, M. M., Zinnerger, N. M., Schiff, L. and Shapiro, N.: *Am. J. Med. Sc.* 205: 328-333, March, 1943.
- Templeton, F. E., and Schindler, R.: *Am. J. Roentgen.* 41: 354.
- Schindler, R., and Baxmeier, R. I.: *Ann. Int. Med.* 13:693, 1939.
- Schindler, R.: *Gastroscopy: The Endoscopic Study of Gastric Pathology*, Chicago; University of Chicago Press, 1937.
- Scheff, H., Horner, J. L., and Kenamore, B.: *Gastroenterology* 3: 506-507, December, 1944.

Luetic Rectal Stricture

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ONLY one conclusion can be reached by scanning the literature on the subject of syphilis of the anus and rectum. This conclusion finds agreement with Buie's (1) statement "probably no individual has had sufficient experience with syphilis of the anus and rectum to be able to prepare a comprehensive account of its clinical and pathologic vagaries." Buie also states that he has seen many ulcerative and hyperplastic lesions of the anus and rectum in patients with syphilis which cleared up with antiluetic treatment but he is still not impressed with the certainty of the diagnosis. One must question many of the reports in the literature when these reports are reviewed critically with the advantages of present day diagnostic methods. Many of the previously reported cases of luetic lesions of the anus and rectum before the advent of the Frei test undoubtedly were not syphilis; the lesions might have been due to more than one venereal infection.

Therefore, we believe our case of luetic proctitis with stricture formation is worthy of presentation. Perhaps the characteristics of our case will be of diagnostic value in the investigation of other similar cases in the future, in spite of the fact that such tertiary lesions will undoubtedly occur less frequently in the future with the present day methods of control and treatment of venereal infections.

CASE REPORT

History.—Mrs. O. K., white, aged 36, consulted a physician for the first time in July 1941. Her main complaints at that time were diarrhea and postprandial abdominal cramps. She had had these attacks for approximately two weeks, having never experienced them prior to this time. These colic-like pains started in the epigastrium and radiated to the lower abdomen but there was no nausea, vomiting or melena. She also complained of "inconous colitis."

The menstrual history was essentially negative. The patient stated that she had leukorrhea for many years. Although she denied ever having a venereal disease, she did state, however, that her first husband with whom she lived for two years was said to have had some such disease. The patient consumed moderate to large amounts of alcohol.

Physical examination revealed a rather well developed, thin, middle aged female who was apparently distressed, apprehensive and under the influence of liquor. The blood pressure was 120/70, pulse 100, temperature 99.2° F.

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Submitted Oct. 6, 1944.

Slight tenderness of the entire abdomen was present and slight spasm of the abdominal muscles was noted. There was no evidence of any tumor mass. The liver and spleen were not palpable and no inginal glands were enlarged. Pelvic examination revealed a marital introitus with a third degree retroverted, small uterus which was fixed posteriorly. Rectal and proctoscopic examination showed no evidence of mucosal ulceration.

Laboratory Data.—The red blood cell count was 3,800,000 per cu. mm. and there was 70% hemoglobin. The white blood cell count was 17,600 per cu. mm. with 43% segmented polymorphonuclears, 22% non-segmented polymorphonuclears, 22% lymphocytes, 7% monocytes, 2% eosinophiles, 1% basophiles, 3% undifferentiated forms. Urine analysis was essentially negative. The blood Kahn test on July 11, 1941 showed a four plus reaction. This reaction was checked on several occasions. The patient refused to submit for spinal tap studies.

Barium meal examination on July 8, 1941 including fluoroscopy of the chest showed no abnormality in the latter. No evidence of a neoplasm nor inflammatory lesion was demonstrated in the esophagus. The mucosal pattern of the stomach along the greater curvature was exaggerated, suggesting hypertrophy of the gastric rugae. There was no evidence of any other abnormality in the esophagus, stomach or duodenum and hourly observations of the small intestines revealed no abnormality.

Barium enema examination was done on July 9, 1944 and revealed a narrowed segment of rectum measuring approximately 3 to 4 inches in length. This lesion appeared to be situated just proximal to the rectal ampulla (Fig. 1). The mucosal pattern was not ulcerated and no obstruction was encountered. Double contrast studies after the injection of air rendered no additional information. The roentgen appearance was consistent with that of a granulomatous lesion of the rectosigmoid and the possibilities considered were luetic proctitis, lymphogranuloma inguinale and lymphosarcoma.

Frei tests were done on July 17 and August 2, 1941 and showed negative reactions on both occasions. Mouse brain antigen (0.1 cc.) was used and controls with normal saline solution were done. Cervical smears were negative for gram-negative diplococci.

Course.—Continuous anti luetic therapy was given over a period of two years (July 1941 to July 1943). Potassium iodide was also given intermittently. The blood Kahn and Wasserman tests were four plus and three plus at the end of the treatment period. The blood count returned to normal.

On January 15, 1942 reexamination of the colon by means of a barium enema (Fig. 2) again demonstrated the constricting lesion previously described but some distensibility was noted. The degree of stenosis was also less marked. The mucosa appeared to be intact (Fig. 3) and no fistulous tracts were opacified. The remainder of the colon was essentially negative.

In November 1943 even more distensibility of the previously described stenotic portion of the rectum was demonstrated (Fig. 4). The edges were smooth



Fig. 1. Barium enema examination done July 9, 1941 shows narrowing of rectum without evidence of mucosal ulceration. No obstruction nor spasm was observed.

and the stenotic segment was shorter. The roentgen appearance at this time, approximately twenty-eight months after the original examination, was considered as representing the end result of the luetic process and fibrosis. Opaque material in both buttocks represented evidence of the previous antiluetic therapy.

The patient has been symptom free since about January 1942; she is in excellent condition at the present time.

ETIOLOGY AND INCIDENCE

The rarity of luetic lesions of the rectum and anus is substantiated by the results obtained by Buie's (1) questionnaire. This questionnaire was sent to twenty leading proctologists each with an average clinical experience of twenty-seven years. These men reported that they saw a total of twenty-five cases of syphilis of the anus and rectum. At the Mayo Clinic (2) not a single case of a primary syphilitic lesion of the anus or rectum was encountered in 40,000 patients with known syphilis. In approximately eighteen years at Bellevue Hospital, New York City, Hirsch (3) saw a tremendous number of luetic lesions. He stated that all of the suspected cases of luetic rectal stricture proved to be lesions caused by other diseases.

Spirochaeta pallida infections involving the anus and

rectum occur in congenital and acquired forms. According to Tuttle (4), 50% of the children born of luetic parents show involvement of the rectal outlet. Feldman (5) states that the jejunum and ileum are affected with greater frequency than the colon in congenital cases.

Feldman (5) claims that the sigmoid and rectum are most commonly involved in the acquired cases. Power and Murphy (6) list the order of frequency of involvement as follows: (1) rectum, (2) jejunum; (3) colon, (4) duodenum, (5) stomach. Brunner and Neuman (7) believe that syphilis of the intestines is more common than syphilis of the stomach while Wile (8) and Mills (9) contend that involvement of the stomach occurs as frequently as involvement of the intestines. At any rate, conclusions based on statistics of such small series cannot be reliable. To add to the confusion, one cannot lose sight of the fact that many of the previously reported cases of luetic infections of the anus and rectum were probably instances of lymphogranuloma inguinale or a combination of venereal infections. The Frei test has, of course, served to remove the condition of lymphogranuloma inguinale from the confusing group of rectal conditions in which granulomatous changes are characteristic.

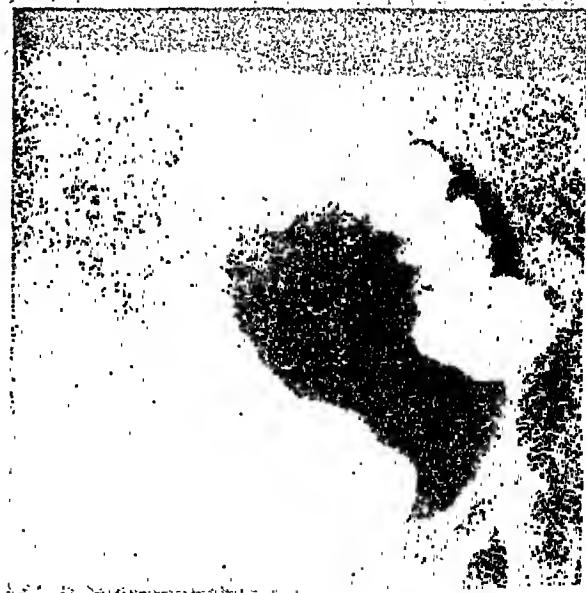


Fig. 2. Examination of January 15, 1942, showing some distensibility and less stenosis. Area of involvement more sharply demarcated—funnel-shaped appearance simulated at both ends of stenotic segment.

PATHOLOGY

The anus and the surrounding tissues, which are epidermal or modified epidermal tissues can be involved in the primary stage of syphilis. The mucous patch of the secondary stage of syphilis occurs in the rectum. The tertiary stage is characterized by the typical perivascular infiltrative process of syphilis. Ault (10) describes the pathology as a diffuse perirectal infiltrating process with subsequent stricture formation and claims that the lumen of the bowel is not usually involved. Rosser (11) asserts that strictures are due primarily to gonorrhea. We believe that the latter is questionable.

Lynch and Hamilton (12) are of the opinion that syphilitic strictures are due to marked secondary infection. Feldman (5) has attempted to classify luetic involvement of the intestines into three groups: (1) catarrhal, (2) ulcerative, (3) gummatoous or tertiary form.

DIAGNOSIS

The diagnosis of luetic stricture of the rectum is not simple and often not conclusive. The mere fact that the complement fixation test is positive does not necessarily imply that the rectal lesion is due to lues. On the other hand, the serology should be positive in a given case where lues is suspected. It then becomes the duty of the attending physician to exclude other etiological factors, i.e., venereal, inflammatory or neoplastic diseases.

Ault (10) states that there is no typical picture of luetic proctitis during proctoscopy. This observation can well be explained by the fact that the mucosa is usually not involved.

Roentgen examination of the colon should include double contrast and follow-up studies, the latter being very important in the differential diagnosis. Engelstad (13), in his report of three cases of luetic stenosis of the alimentary canal, describes these lesions thusly:

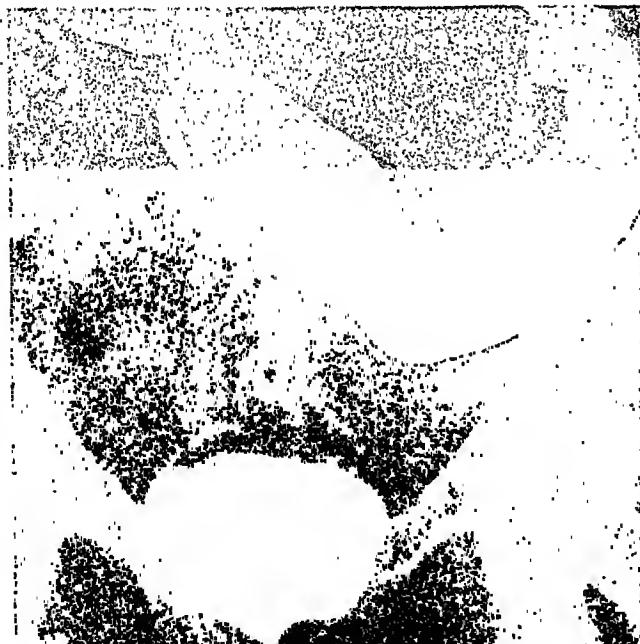


Fig. 3. Double contrast visualization after injection of air (January 15, 1942) shows no evidence at mucosal ulceration. Slight distortion of mucosal pattern as the result of submucosal fibrosis.

"... transformation of the lumen into a narrow, rigid tube, which widens out evenly, without ridge-like demarcation, above and below the contracted part. The contours are smooth and even." Lewis (14) describes a luetic stricture as a "... long, narrow, small, fusiform, rigid channel, fading gradually into an undilated hypertrophied colon above. Both ends portray a funnel appearance." Gatewood and Kolodny (15) state that the appearance of the lesion, except those in the sigmoid and rectum, is scarcely distinctive. In the distal colon,

however, the sigmoid or rectum is tubular, narrow and smoothly stenosed. Spasm is rarely observed.

The differential diagnosis must include numerous conditions, the most important of these being the venereal strictures. If gonorrhreal proctitis is suspected search for gram negative diplococci should be made. In some cases it is impossible to differentiate between lues and lymphopathia venereum. It should also be emphasized that more than one venereal disease can be present in the same patient.

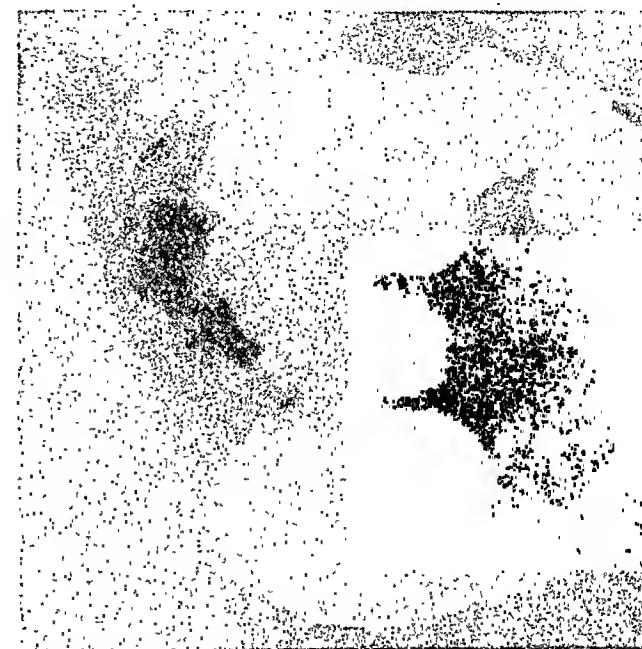


Fig. 4. Examination on November 19, 1943, demonstrates end result of luetic process in rectum. The residuum of the luetic involvement is represented by a constriction. Opaque material in the soft tissues represents evidence of the previous antiluetic therapy.

Poppel (16), who has observed about 200 cases of rectal venereal lymphogranuloma, states that the Frei test is almost always positive in this condition, especially if the test is repeated. The tests will be positive if there is any active inflammation and if the test material is fresh. Ault (10) agrees that the Frei test remains positive for life. Klein (17) in a recent report, on the other hand, cites some cases which showed negative Frei test reactions. In this condition there is destruction of the mucosa, rectal stricture, sinus and fistula formation. This disease usually runs a chronic course, often lasting twenty years or more. The other clinical manifestations of lymphogranuloma inguinale are important in the differential diagnosis. The clinical picture varies with the sex of the patient. In the male, the primary lesion occurs on the penis and the lymphatic drainage is directed to the inguinal regions. When the primary lesion in the female occurs on the vulva the lymphatic vessels lead to the perirectal region. Therefore, this type of venereal stricture occurs more frequently in women. Such a stricture never improves (Poppel (16)) and is rarely affected by antiluetic treatment (Bloom (18)).

The majority of carcinomatous lesions of the rectum

occur on the anterior wall of the rectum and the clinical course is, of course, much shorter than lymphogranuloma venereum. Lymphosarcoma of the rectum must also be considered and excluded in the differential diagnosis. Biopsy will provide the necessary information.

Diverticulitis usually occurs at the junction of the descending and sigmoid segments of the colon. Diverticulitis and carcinoma can and not infrequently occur together and can often be confusing. Ulcerative colitis involving the rectum can, of course, occur. Evidence of mucosal ulceration must be present either by contrast or proctoscopic examination or both.

Interest in the condition of endometriosis of the rectum and sigmoid has justly and recently been revived by Jenkinson and Brown (19) who have emphasized that endometriosis is a prominent etiological factor in the differential diagnosis of a constricting lesion of the rectosigmoid. This condition must be considered in women during their active menstrual period. Castration by means of x-ray, of course, cures the condition. Radiographically these lesions are sharply demarcated and the other portions of the colon show no definite abnormality.

REFERENCES

1. Buie, Louis A.: Practical Proctology, W. B. Saunders Co., Phila., 1938.
2. Quoted by Buie.
3. Hirsch, I. S.: Quoted by Poppel in personal communication.
4. Tuttle, H. K.: Syphilis of Jejunum, *Surgery, Gynecology and Obstetrics*, 55:518-522, October 1932.
5. Feldman, Maurice: Clinical Roentgenology of the Digestive Tract, William Wood and Company, Baltimore, Md., 1938.
6. Power and Murphy: Quoted by Feldman.
7. Brunner and Neumann: Quoted by Feldman.
8. Wile, U. J.: Quoted by Feldman.
9. Mills, R. W.: Quoted by Feldman.
10. Ault, G. W.: Venereal Diseases of Anus and Rectum, *American Journal of Syphilis, Gonorrhea and Venereal Disease*, 21:430-455, July 1937.
11. Rosser, C.: Venereal Infections of Anus and Rectum, *Texas State Journal of Medicine*, 29:390-395, October 1933.
12. Lynch, J. M. and Hamilton, G. J.: Syphilis of Caudal Bowel, *Urological and Cutaneous review*, 43:79-80, January 1939.
13. Engelstad, R. B.: Luetische Stenosen im Verdauungstrakt, *Acta Radiologica*, Vol. XIII, 249-263, 1932.
14. Lewis, D. S.: Medical Clinics of North America, 7: 1925, 1924.
15. Gatewood, W. E. and Kofodny, A.: *American Journal of Syphilis*, 7: 648, 1923.
16. Poppel, M. H.: Personal communication.
17. Klein, I.: Roentgen Studies of Lymphogranuloma Venereum, *The American J. of Roentgenology and Radium Therapy*, 51: 70-75, January 1944.
18. Bloom, David: Stricture of Rectum Due to Lymphogranuloma Inguinale, *Surgery, Gynecology and Obstetrics*, 58: 827, May 1934.
19. Jenkinson, E. L. and Brown, W. H.: Endometriosis, *The Journal of the American Medical Association*, 122:349-354, June 5, 1943.

Differential Diagnostic Problems in Diseases of the Mesenteric Glands

By

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DIAGNOSIS has always been and always will be the outstanding problem in diseases of the abdominal organs and systems. The multiplicity of organs found in the abdominal cavity and surrounding regions explains the difficulties with which the physician is confronted. Considering the various pathological changes as due to inflammation, tumor growth, displacement of organs and innumerable other forms of pathology, we realize how important and also how difficult correct

diagnosis, previous to correct therapeutic procedure, is. In establishing the correct diagnosis of so-called intra-abdominal diseases, we should never forget the proximity of the retroperitoneal systems. Both the intra- and the retro-, or extra-peritoneal systems may have the same nervous segmentation and by this common innervation may increase the difficulty of establishing the right diagnosis.

All forms of pathology, of which the above mentioned inflammation, tumor growth, displacement of

organs, etc., are only a very few examples, may be found equally in all organs of the intra-peritoneal and extra-peritoneal spaces. Additional difficulties may arise from farther-distant organs, with pain and sensation radiating toward the abdomen. We know that intra-thoracic diseases as, for instance, angina pectoris, may radiate toward the abdominal organs and may be perceived and localized intraperitoneally. Inflammatory, degenerative and other processes of the legs may, on the contrary, radiate toward the abdomen and simulate primary involvement of intra- or extra-peritoneal organs. Inflammation and thrombosis of the veins of the lower extremity may cause only minor local signs and symptoms and may appear under the picture of acute inflammatory disturbance of an abdominal organ. Other extra-abdominal organs like testicles, epididymes and spermatic cords may simulate acute peritonitis symptoms.

The diseases of the genito-urinary system, in all its parts, may produce the confusing picture of any intra-peritoneal pathology. The radiating pain characteristic of diseases of the urinary organs may be entirely absent or may radiate rather toward the intra-abdominal organs than down to the bladder and scrotal contents. Nothing can be more difficult, even to the most experienced physician, than differential diagnosis between genito-urinary and intra-peritoneal organs. Only the most exact check up with all well known laboratory methods, with x-ray of gastro-intestinal and urinary systems may enable us to establish the diagnosis as to which organs are involved. Complete cystoscopy, including functional tests of the kidneys by injection of dye, catheterization of the ureters, collecting of split specimens of urine from both kidneys, and retrograde pyelography may succeed in establishing the right diagnosis and eliminating doubts concerning the organs primarily involved.

Hardly any part of the abdominal regions is more often affected by diseases and produces more differential problems than the right lower abdominal quadrant. In addition, the fact remains that any pathology involving the right lower extremity may radiate, as mentioned above, into the right lower abdominal region. This region may be the center of trouble for pathological processes originating from the genito-urinary and intra-peritoneal organs. The female genital organs, in the light of our problem, have to be considered as being intra-peritoneally situated. Special problems and enormous difficulties may arise in cases of diagnosed or unknown situs inversus. Left-sided appendicitis may simulate all forms of gastro-intestinal or genito-urinary diseases in both male and female. It may be impossible to differentiate left-sided appendicitis from any left-sided urinary disease complicated by hematuria. If, in addition, we think of the well-known fact that in retro-cecal position of the appendix we may find pure hematuria in acute appendicitis, we realize that it can be extremely difficult to establish the correct diagnosis. Retro-cecal position of an inflamed appendix may cause peri-ureteritis and ureteritis, both making hematuria and simulating a disease of the urinary system.

A special problem in all diseases of acute and chronic character involving organs and neighborhood of the right lower abdominal quadrant is presented by the various glands found in this region. The so-called ileo-cecal or mesenteric glands in this region undergo all the primary and secondary pathological features of the glands all over the body. Glands of any region may, primarily or secondarily, be the cause of considerable pathological changes. The process of this specific disease may be either of chronic or of acute character. And, to make the problem even more complicated, the mesenteric glands of the right lower abdominal quadrant may still be the cause of disturbance after the acute or chronic disease has subsided.

The structural changes of glands going through an acute or chronic disease, primarily or secondarily, already carry in itself the dangers and complications resulting from a so-called healed glandular involvement. The tendency of healing, in glandular involvement, means the shutting off and sealing of the glands from general circulation. Mostly we have to deal with multiple glands in the ileo-cecal region which, as long as they are not diseased, appear as small, often invisible, isolated structures. The acute or chronic disturbance of these normally isolated and independent lymph glands causes an enlargement and swelling of the individual nodes. The resulting, often enormous, mass of enlarged glands, may appear as an inflammatory swelling or real tumor-like growth of considerable extent.

What are the changes inside of such an inflammatory or tumor-like glandular mass? In many acute cases the resulting mass of glandular inflammation may soften and produce a glandular abscess in the abdominal cavity. The further fate of the ensuing pus is determined by both the rapidity and the virulence of the infection, as well as by the ability of the surrounding tissues to build up a protective wall against the pus. A very acute inflammation of the mesenteric glands may liquefy and perforate into the intra-abdominal cavity, or towards the kidneys, ureters or the retro-peritoneal space. In these very acute cases, the neighboring organs and the surrounding soft tissue have no time to build up a strong protective wall against the glandular abscess. Circumscribed and even diffuse peritonitis involving the open abdominal cavity may result, as well as emptying of the pus through the ureters into the bladder if the perforation pointed toward kidney or ureter.

Chronic inflammation and involvement of mesenteric glands in the ileo-cecal region may have many reasons. Practically every disease which in its course is apt to involve lymph glands may also affect the mesenteric glands in the right lower abdominal region. Various blood dyscrasias with participation of the glandular system affect also the lymph glands of the ileo-cecal region. Isolated swelling of these glands may occur in chronic inflammatory diseases of the gastro-intestinal system, just as the regional glands all over the body enlarge in chronic inflammation of the organs of which these respective glands are the filter.

A special picture which should draw special atten-

tion in this respect is the tuberculosis of the mesenteric glands. There is no doubt that, as all over the body, also the regional ileo-cecal glands may enlarge as a sequence to gastro-intestinal tuberculosis. But there is no question that isolated ileo-cecal enlargement on a tuberculous basis is rather the exception than the rule. It may happen, and it certainly does happen, that in primary gastro-intestinal tuberculosis on nutritional basis primarily the right lower abdominal mesenteric glands are enlarged. But mostly, and especially in infants and children, both the hilus and the right lower abdominal mesenteric glands will be found enlarged in tuberculosis.

The ultimate fate of an acute glandular inflammation may be a restoration of the involved glands, without leaving any trace as far as can be recognized by x-ray examination or by palpation. Acute, mostly purulent glandular inflammation may heal with a relatively small scar, under the destruction of the gland and its vital function, but without any immediate interference with the neighboring organs. The final fate of chronic glandular inflammation is different. The chronic process both in tuberculous and non-tuberculous diseases does not radically destroy the glandular tissue as much as in acute glandular inflammation with pus formation. The slow chronic infiltration of these glands permits the gland to react and to produce protective walls against the inflammation throughout the glandular body and around it. Encapsulated, ensheathed portions and fidae of the gland remain and undergo a slow but continuous change toward replacement of the glandular tissue by calcification. The final fate, as in most chronic glandular diseases, is a calcified mass, replacing the site of normal glandular tissue. Of course, also, in chronic, especially tuberculous, glandular inflammation in the ileo-cecal region the glands may liquefy. It may even come to a perforation into the neighboring organs, to sinus or fistule formation. These canals may become mixed-infected from the gastro-intestinal system and may lead to abscess formation of the gland. As a rule, we find after chronic glandular inflammation calcified masses in the ileo-cecal region, which can be recognized by x-ray. In infants and children they may be easily palpated as a hard, tumor like mass in the right lower abdominal quadrant.

What are the clinical effects of the above-described glandular disorders in the ileo-cecal region? As far as acute destruction is concerned, there may be none, because the glands may more or less disappear without leaving any trace, without secondary influence upon the nearby organs and without becoming later on the problem of ensuing pathology. Since glands after acute inflammation hardly ever calcify they mostly cannot be visualized by x-ray and will not appear as tumor masses.

The scars left after chronic destruction, either tuberculous or non-tuberculous in the ileo-cecal region, frequently present diagnostic difficulties. It should not be forgotten that, especially in infants and children, calcified tumor masses of destroyed mesenteric glands are already a disease in itself. The accompanying sinus

or fistula formation, the displacement by scars extending into the mesenteric, or even into, the intestines, may produce pain, tenderness, disturbance of bowel movement and all the other signs and symptoms of chronic gastro-intestinal disorder. Intestinal obstruction caused by pressure of the tumor masses upon the intestinal loops or by scar traction, may present a very severe problem. Diagnosis can be established by both palpation of glands as well as X-ray visualization of intestinal obstruction.

The most frequent differential diagnostic problem and resulting error in diagnosis is the question of chronic or acute appendicitis. There is no doubt that the appendix may very frequently be involved secondarily after primary ileo-cecal glandular disease. As with all intestine, the cecum and the appendix may be pushed away by glandular masses or fixed by scar formation between glands and cecum or appendix. In chronic cases X-ray examination may reveal the presence of calcified glands in the ileo-cecal region, and the secondary involvement of the appendix. The appendix may not be filled at all in either the oral or rectal application of the barium, the appendix may be visualized, but may not empty after a laxative, due to regeneration and scar formation in its mucous membrane. There is no doubt that such a finding deserves the name of (secondary) chronic appendicitis. The patient may be relieved from his pain and disability by an appendectomy, but we should not forget that an appendectomy in such a case is rather unsatisfactory, leaving the glandular masses in the abdominal cavity untouched. It is not advisable to go in and try to remove the glandular mass found in a laparotomy. Partial resection of these calcified glands opens encapsulated and apparently harmless parts of the gland, causing discharge, with all the risks involved. A radical resection of the calcified mass is a major operation, with little hope for permanent cure. The frequent ramification and the involvement of vital organs of the posterior abdominal wall may result in severe damage after the attempt to remove these mesenteric glands. If an operation (besides the relatively harmless appendectomy in secondary appendicitis) has to be performed for intestinal obstruction caused by calcified mesenteric glands, the surgeon has to be prepared for resection of large parts of the intestines together with the glands. The proximity of the right ureter may complicate this dangerous operation.

Differential diagnosis problems may arise concerning the intra-or retro-peritoneal location of X-ray shadows. Shadows in the right lower abdominal region may appear on flat plates. It is often extremely difficult to make an exact diagnosis whether the shadow in question is an ileo-cecal gland or a ureter calculus. The X-ray shadow of a stone very often, but not always, is dense in the center and light in the periphery, whereas the X-ray picture of calcified glands often shows the periphery as a dense, protective wall around a light center. Frequently exact diagnosis as to the organs involved can only be made by intravenous urography or retrograde pyelography. A stone in the ureter may show dilatation of the kidney and the ureter

above in intravenous urography. The tip of the catheter introduced through the cystoscope can be pushed up to the suspicious shadow. But especially under spinal anesthesia and complete relaxation the catheter may be brought up above the questionable shadow. The localization can be difficult, even under cystoscopy. We should not forget that extra-ureteral shadows may compress the ureter and cause a stricture of the ureter. Such an extra-ureteral shadow, too, may show the ureter and kidney dilated, may stop the tip of the catheter and may simulate the clinical picture of a ureter calculus. In opening up and exploring for the stone

assumed to be in the ureter, we then realize that we are dealing with calcified glands of the ileo-cecal region and the posterior peritoneal wall, producing all the signs and symptoms of a ureter calculus.

There is no doubt that problems arising from and dealing with glandular swelling, enlargement and calcification in the right lower abdominal quadrant are multitudinous. The present discussion can only be an outline and a renewed hint that all specialties have to cooperate in establishing the right diagnosis and suggesting the proper therapy.

Summaries of Current Literature From Axis Countries

Brief summaries of papers dealing with gastroenterology which have been published in enemy and occupied countries from 1941 to date will be presented in this journal as they become available. These are prepared by the staff of abstractors. It is to be borne in mind that very likely much of the research reported during this period was actually done before commencement of hostilities. It is also to be remembered that numerous research studies carried out by the enemy during the war have not been published for reasons of military necessity.

Akitake, A. Action of picrotoxin on stomach and colon of the rabbit. *Japan. J. Med. Sci., Sect. IV, Pharmacol.*, v. 4, p. 37, 1941. (Japanese)

Picrotoxin given intravenously to rabbits under urethane anesthesia inhibited the movements of the colon and stomach. The effect is not abolished by vagotomy. Stimulation of the sympathetic nerve centers is believed responsible.

Baclasses, F. Roentgenotherapy of glossoepiglottic epitheliomas. *J. Radiolog. Electrolog.*, v. 25, p. 190, 1942. (French)

Results on 256 patients treated at the Curie Foundation during 1920 to 1938 are reviewed. Twenty per cent of the cases in which cancer was still localized were cured but only 3 per cent of the cases were cured when the cancer had already invaded other organs. Patients with interstitial cancer were incurable.

Balint, P., and Balint, M. Chemical composition of blood proteins from anemic patients. *Biochem. Zeitschr.*, v. 315, p. 41, 1943. (German)

No relationship between blood plasma proteins or the amino acids of the proteins and the type of anemia was found. The range in values for normal plasmas and anemic plasmas overlap.

D'Ambrosio, L. Lipemia in experimental pancreatic diabetes. *Folia med.*, v. 29, p. 329, 1943. (Italian)

Cortical hormone reduces the lipemia in both human diabetes and in experimental pancreatic diabetes. The action is due to the inhibition of fatty infiltration of the liver and decrease in the diabetic hyperlipemia.

Deschiers, R., Decourt P., and Provost, A. Experimental colitis and insoluble bismuth salts. *Presse med.*, v. 51, p. 450, 1943. (French)

Cats developed colitis 3 days after *B. coli* cultures were introduced into the intestine. The disease lasted 25 days and the mortality was 25 per cent. Bismuth subnitrate reduced the mortality to zero and cut the length of time of illness.

Gotsev, T. Does the splanchnic region act as a single functional unit? *Arch. exptl. Path. Pharmakol.*, v. 201, p. 172, 1943. (German)

Autonomic drugs such as epinephrine, ephedrine and acetylcholine, as well as other drugs such as nicotine and histamine, were administered. Experiments with spinal cord section were also performed. Since the response of the visceral organs of the splanchnic region was different for each stimulus it was concluded that the whole splanchnic region acts as an anatomical but not a physiological unit.

Gugliucci, A. Chlorine metabolism in patients with gastric disorders. *Folio med.*, v. 29, p. 222, 1943. (Italian)

Histamine given subcutaneously caused a lowering in the venous blood chloride level in normal people and patients with gastric pathology whose gastric acidity values were normal or low. In cases of hyperchlorhydria the venous blood chloride was found to be higher than normal.

Horiuti, K., and Kurosu, V. Anthelmintic action of phenylthiourethane. *Jap. J. Med. Sci., Sect. IV, Pharmacol.*, v. 14, p. 12, 1941. (Japanese)

Hog ascarides were killed by 0.5 to 0.1 per cent solution of phenylthiourethane. Given to puppies in doses as large as ten times the usual dose of santonin it was non-toxic and had a moderate vermisuge action.

Huchtemann, T. The influence of the nature of dietary protein on the liver glycogen content. *Biochem. Zeitschr.*, v. 308, p. 40, 1941. (German)

Amino acids have a direct effect on the liver glycogen content. This effect is not exerted thru the action of the amino acids on oxidative processes.

Jensen, H. B. and Wanscher, O. Influence of ethyl alcohol ingestion on vitamin A deposition in the rat liver. *Vitamine u. Hormone*, v. 2, p. 27, 1942. (German)

Less vitamin A was deposited in the rat liver when alcohol was given by stomach tube than when alcohol was not given. Animals receiving alcohol showed decrease in weight.

Kabitz, G. Serum lipase and nutritional experiments. *Biochem. Zeit.*, v. 316, p. 409, 1944. (German)

In humans as well as dogs the serum lipase level was not increased when either natural or synthetic fats were fed except in extremely large amounts.

Kotsonsky, D. Biochemistry of bile in relation to age. *Wien. klin. Wochenschr.*, v. 55, p. 269, 1942. (Austrian)

Bile from older animals can emulsify olive oil more readily than bile from younger, tho both biles emulsify mineral oils equally readily. Old animal bile contains more mucin than young animal bile. Young ox bile when dried at room temperature shows no crystals but old ox bile shows a distinct crystal pattern when dried.

Kraut, H., Weischer, A., and Hugel, R. Hydrolysis of fats by pancreatic lipase. *Biochem. Zeitschr.*, v. 316, p. 96, 1943. (German)

A number of fats were studied with respect to their ability to be hydrolyzed by pancreatic lipase. The smaller the molecular weight of the triglyceride used the greater was the extent of hydrolysis. Synthetic and natural-occurring triglycerides were equally well hydrolyzed.

Marche, R. and Siede, W. Differential diagnosis of icterus catarrhalis and of hepatitis epidemica. *Munch. med. Wochenschr.*, v. 89, p. 923, 1942. (German)

Three groups are distinguished. Group 1, specific icterus catarrhalis, results in toxic edema of the liver and destruction of liver cells. Group 2, capillary cholangitis, is either hematogenous or is due to ascending biliary infections. In Group 3, specific hepatosis, there is direct destruction of the liver cells by toxins (arsenicals, chloroform, etc.).

Muller, R., Edelmann, K. and Kuhn, K. Substances for treating hyperacidity. *Munch. med. Wochenschr.*, v. 89, p. 423, 1942. (German)

The change in pH of gastric contents produced by different ant-acids is shown. Compounds of magnesium, bismuth and aluminum and sodium bicarbonate were studied.

Onaka, M. Action of tetrahydro-B-naphthylamine in the digestive tract. *Jap. J. Med. Sci., Sect. IV, Pharmacol.* v. 14, p. 38, 1941. (Japanese)

Tetrahydro-B-naphthylamine given parenterally increased the motor activities of the stomach and intestine of anesthetized rabbits.

Rhode, H. Analgesia and spasmylosis. *Fortschr. Therap.*, v. 19, p. 189, 1943. (German)

Determinations were made on the frog stomach and rabbit intestine of the spasmyolytic action of a number of drugs, including cocaine, procaine, codeine, morphine, papaverine and benzylbenzoate. The spasmyolytic effect of a drug was found to be related to its analgesic action.

Seitz, W. Testing gall bladder contraction with mannitol and sorbitol in cholecystography. *Klin. Wochenschr.*, v. 22, p. 519, 1943. (German)

The human gall bladder, rendered visible by radio-opaque substances, will contract following ingestion of mannitol or sorbitol. The effect is similar to the so-called egg-yolk motor meal. Other sugars are only slightly if at all effective.

Sibata, S. Influence of various amino acids on the reaction of the intestine to histamine. *Jap. J. Med. Sci., Sect. IV, Pharmacol.*, v. 14, p. 32, 1941. (Japanese)

Natural arginine, histidine and cysteine counteracted the stimulatory effect of histamine on the isolated intestine of the guinea pig. Little or no inhibitory effect was obtained in isolated rabbit intestine.

Siede, W. and Leitz, K. Etiology of epidemic hepatitis: cultivation of a virus. *Klin. Wochenschr.*, v. 22, p. 70, 1943. (German)

By inoculation of chick eggs with fresh duodenal contents from patients with epidemic hepatitis a filtrable virus was isolated. Cultivation of the virus was successful only if the duodenal juice was fresh and immediately transferred to the egg. The virus appeared particularly concentrated in the liver pulp of the dead chick embryo.

Ufer, J. Spontaneous hypoglycemia. *Deutsche med. Wochenschr.*, v. 69, p. 206, 1943. (German)

A female patient suffered spontaneous bouts of hypoglycemia, the blood sugar going down to as low as 20 milligrams per cent. Recovery ensued after removal of a myosarcoma of the uterus. The author suggests that the tumor had a hormonal activity which stimulated the islands of Langerhans with the resulting production of hypoglycemia.

von Bakoy, L. Regeneration of islands of Langerhans. *Arch. path. Anat. Physiol.*, v. 310, p. 291, 1943. (German)

The islands of Langerhans are capable of intense degrees of regeneration. Old island cells may segment so that fission gives rise to new cells. Or new island cells may be formed by transformation of the acini. Regeneration to some extent has been found in all cases of diabetes and may be sufficiently great to lead to absence of all symptoms.

Samuel Weiss M.D., F.A.C.P.

ON HIS SIXTIETH BIRTHDAY ANNIVERSARY

By

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DR. SAMUEL WEISS who is Clinical Professor of Gastroenterology at the New York Polyelnic Hospital and Post-Graduate Medical School, was born May 6, 1885, in Hungary, the son of Jacob and Nina Weinberger. He received his M.D. degree in 1907 from Long Island College Hospital. He studied in the United States and in Vienna and other European clinics. On January 11, 1914, he married Ella Margaret. He has three children, Daniel, Dr. Jerome (physician) and Bernard, all at present in United States Army service.

Dr. Weiss began practicing as a physician in 1907 and served in several out-patient department clinics. He became attending gastroenterologist of the Jewish Memorial Hospital in 1918. He has served as Adjunct Professor (1925), Clinical Professor and Chief of the Clinic of the New York Polyelnic Medical School and Hospital since 1927. He is Consulting Gastroenterologist to the Beth David Hospital and the Long Beach (Long Island) Hospital and several others. He is a Life Fellow of the American College of Physicians and a Fellow of the American Medical Association. He is a Fellow of the Gastro-enterologique de Paris, the Belgian Gastro-enterologic Society and is a Diplomate of the American Board of Internal Medicine. He has been editor of the Review of Gastroenterology since 1934 (March). He is past-president of the Medical Board of the Jewish Memorial Hospital and of the American-Hungarian Association. He has been a very active Founder Fellow of the National Gastroenterological Association. He is a member of the International Society of Gastroenterology (Brussels), Jewish Academy of Arts and Sciences, the International Medical Club, the New York County and State Medical Societies. He was decorated Chevalier of the French Legion of Honor. He is Surgeon, U.S.P.H.S. (R), and Examining Physician for the Veterans Rehabilitation of Selective Service and War Manpower Commission. Dr. Weiss has published about fifty medical papers and has made numerous contributions to textbooks, journals, conventions, international congresses and local medical society meetings. He is the author of *Diseases of Liver, Gallbladder, Ducts, and Pancreas*, a book of 1100 pages published in 1935; *Clinical Lectures on the Gallbladder and Bile Ducts*, a volume of 504 pages published in 1944. It is a privilege and pleasure indeed to have known Dr. Weiss for many years and to have met him and his family socially and to have collaborated with him in a number of interesting problems. I am happy to submit these few remarks as a partial and incomplete biographic sketch of my friend and colleague, Dr. Samuel Weiss, and to congratulate him and to wish him well on this his sixtieth birthday anniversary. Appended to these is a partial list of Dr. Weiss's publications.

Publications by Dr. Weiss.

Diverticula of the Stomach. *Med. J. and Record*, N. Y., 121:768-770, June 17, 1925. Presented before the Clinical Society of the Jewish Memorial Hospital, Jan. 6, 1925 (Xray films).

Herpes Zoster with Unusual Prodromal Symptomis; with report of a case. *Med. J. and Record*, N. Y., 124:761-762, Dec. 15, 1926. Presented before the Society for Clinical Study, N. Y., on January 26, 1926.

Unrotated ascending colon and cecum with appendicular abscess. *Med. J. and Rec.*, 130: 563-564, Nov. 20, 1929. (Case came under his observation in Feb. 1927—41 year old woman).

Acute Yellow Atrophy of Liver; Acute necrosis of liver. *Med. J. and Rec.*, 135: No. 7, 316-321, April 6, 1932.

Newer Synthetic Drugs in Treatment of biliary diseases. *Med. J. and Rec.*, 137: 197-201, March 1, 1933.

Evaluation of efficacy of oleic acid with bile salts in enterohepatic disease; clinical experiment with 25 subjects. *J. Lab. and Clin. Med.*, 18: 1016-1023, July, 1933.

Diathermy as aid to cholecystography. *Arch. Phys. Therapy*, 14: 591-592, Oct. 1933.

Liver Deaths and their prevention; how danger can be recognized and avoided by use of preoperative and postoperative diagnostic measures. *Am. J. Surg.*, 23: 96-101, Jan., 1934.

Weiss and Collins, V. L., Role of Vegetative Nervous System in gastrointestinal disease; vagotonia and sympatheticonia; clinical study. *Internat. Clinics*, 1: 107-131, March, 1934.

Dietetic and Hygienic Management of Cholelithiasis. *Med. Rec.*, 141: 568-571, June 19, 1935.

Portal Hypertension (hepatic decompensation); critical study of circulatory system of liver and evolution of syndrome of portal hyperextension. *Internat. Clinics*, 1: 148-194; March 1936.

Large Penetrating ulcer on lesser curvature of stomach; report of case treated by injections of histidine (larostidin) with 9 months follow-up. *Med. Rec.*, 144: 304-306, Oct. 7, 1936.

I. W. Held—Dedication in honor of his Sixtieth Birthday. *Rev. Gastroenterol.*, 3: 345-347, December, 1936.

S. Weiss and W. B. Rawls and V. L. Collins. Liver Function in Rheumatoid (chronic infections) arthritis; (preliminary report). *Ann. Int. Med.*, 10: 1021-1027, Jan., 1937; 12: 1455-1462, March, 1939.

Physical therapy in Gastritis. *Med. Rec.*, 147:68-71, Jan. 19, 1938.

Medical and surgical jaundice with consideration of liver deaths. *Internat. Clin.* 1: 96-114, March, 1938.

Preoperative and Post-operative medical management of biliary conditions. *Med. Rec.*, 150: 311-316, Nov. 1, 1939.

Ascites. (Intraperitoneal fluids); anatomic, physiologic, neurologic and mechanical causes; diagnosis. *Internat. Clin.*, 4: 162-195, Dec. 1939.

Medical Treatment of Liver and Gallbladder Diseases. *Med. Rec.*, 153: 398-404, June 4, 1941.

S. Weiss, A. Slatiger, and S. Goodfriend. Relation of nasopharynx to ulcerative colitis; preliminary report. *J. Lab. and Clin. Med.*, 36: 1925-1927, Sept. 1941.

Gastro-intestinal disturbances secondary to disease of genito-urinary organs. *Urol. and Cutan. Rev.*, 46: 213-217, April, 1942.

S. Weiss and M. Fabricant. Clinical Studies on urinary excretion of bisulfite binding substances. *Med. Rec.*, 155: 51-54, Jan. 21, 1942.

S. Weiss and E. Foldes. Digestive System and Blood: inter-relationship between digestive system and morphologic and chemical composition of blood. *Internat. Clin.* 1: 234-254, March, 1942.

New and Inexpensive Apparatus for rapid estimation of icterus index by means of graduated color scale; no standard required. *Med. Rec.*, 155: 507-508, Nov. 1942.

Gallbladder Disease and Arthritis. *Review Gastroenterology*, 11: 116-120, March-April, 1944.

ADDITIONAL PUBLICATIONS

1. Gastric and Duodenal Ulcers. Diagnosis and Treatment. N. Y. Med. Jour., 104: No. 25, 1193-1197, Dec. 16, 1916.
2. Gallstones. History, Diagnosis, and Medical Treatment. N. Y. Med. Jour., 107: No 20, 932-936, May 18; No. 21, 980-984, May 25; No. 22, 1022-1028, June 1, 1918.
3. An Open Safety Pin Swallowed by an eight-months old child, and passed through the rectum after four days. *Med. Rec.* 96: No. 5, 189, Aug. 2, 1919.
4. The Medical Treatment of Gallbladder Affections. N. Y. Med. J., 110: No. 5, 187-189, Aug. 2, 1919.
5. The Modern Medical Treatment of Chronic Ulcer of the Stomach and Duodenum; with Special reference to the Sippy Method. *Med. Rec.*, 96: No. 22, 867-873, Nov. 29, 1919.
6. Reflex Symptoms in Gall-stone Disease. Charlotte Med. J., 80: No. 5, 188-189, November, 1919.
7. The Prophylaxis and Treatment of Gall-stone Disease. *Med. Rec.* 97: No. 21, 869-872, May 22, 1920.
8. The Duodenal Tube in Diagnosis and Treatment of Gall-bladder and Biliary Disease. Western Med. Times (Denver), 39: No. 12, 467-470, June, 1920.
9. Ulcer of the Esophagus. Diagnosis and Treatment. N. Y. Med. J., 112: No. 1, 29-30, July 3, 1920.
10. The Nonsurgical Drainage of the Gallbladder as an Aid in the X-ray Diagnosis of Gallstone Disease. N. Y. Med. J., 114: No. 5, 297-298, September 7, 1921.
11. Roentgenoscopy as a Cause of Menstrual Disturbance. N. Y. Med. J. and Record, 118: No. 1:48, July 4, 1923.
12. Diverticula of the Stomach. *Med. J. & Rec.* (supp.), 121: 768-770, June 17, 1925.
13. The Rectal and Duodenal Administration of the Sodium Salt of Tetrabromi-phenolphthalein. A Preliminary Communication. Amer. Medicine, n. s. 20: No. 3, 161-163, March, 1925.
14. The Rectal, duodenal and oral use of sodium salt of tetrabrom-phenolphthalein and tetraiodophenolphthalein. *Med. Klinik (Berlin, Prag. u. Wien)*, 22: No. 28: 1073-1074, July 9, 1926.
15. Achyilia Gastrica. Amer. Med. n. s. 22: No. 2, 79-93, Feb. 1927.
16. Cholecystography and Biliary Drainage as Aid in Diagnosis of Gallstones and Gallbladder Disease. M. J. and Record, 125: 264-265, Feb. 16, 1927.
17. Epidermoid Carcinoma. Ural. & Cutan. Rev. 31: No. 8, 487-488, Aug., 1927.
18. History of Gall-Tract and Biliary Disease. *Med. Life*, 34: No. 12, 663-676, Dec. 1927.
19. Clinical Effects of Lead in Treatment of Malignant Disease. N. J. Record, 127: No. 6, 308-310, March 21, 1928.
20. Gastrophotography; Gastrocaniera, A New Apparatus for Photographing Interior of Stomach. M. J. and Record, 129: 390-391, April 3, 1929.

Book Reviews

The New York Hospital. By William L. Russell, M.D., pp. 556, (\$7.50), New York, The Columbia University Press. 1945.

This is an intensely interesting, beautifully written history of the psychiatric service of The New York Hospital from 1771-1936. Dr. Russell, as is well-known, is Emeritus Professor of Psychiatry, Cornell University Medical College, and was director of the department of psychiatry at the time of the establishment of The New York Hospital-Cornell Medical College Association in 1927. Today, the Payne Whitney Psychiatric Clinic, established in 1932, stands as the final expression of New York City's decades of effort aimed at helping the mentally-ill patient. The book will prove invaluable to those who are especially interested in the subject of the evolution of a psychiatric service which really began toward the end of the eighteenth century, suffered many transplantations from one hospital building to another but always remained

an integral part of that very ancient institution.—The New York Hospital, and finally became domiciled in the staggering aggregation of buildings which today is known as The New York Hospital and Cornell University Medical College. Psychiatry as practiced today is scarcely recognizable as a growth from its primitive prototype, but it is pleasant to learn that from the early days of the eighteenth century, New York City invariably felt moved to do all in its power—(and this at first was very little) to help the mentally afflicted. The book, incidentally, presents an excellent running account of psychiatry, from the days when it was a function of the general practitioner and insanity was believed to be somatogenic and curable, to the present when the field is divided into separate specialties, and insanity is less confidently explained and less optimistically approached. This book must remain an archive of information since it covers periods concerning which no previous organized records existed.

Radiological Examination of the Small Intestine.
By Ross Golden, M.D., pp. 239. (\$6.00), Philadelphia, J. B. Lippincott Company, 1945.

The small intestine has for some time been recognized as the physiological "dark continent" of the digestive tract. Just as physiological studies continue to emphasize and, in a measure, explain why the small gut possesses such great digestive importance, so radiologic studies have assisted in the recognition of serious lesions in the small bowel in advance of surgery. Today, in virtue of the advances made in X-ray studies of the jejunum and ileum, the clinician is less ignorant of events in this inaccessible division of the tract. Inflammatory and neoplastic lesions, granulomata, obstructions, herniae, intussusception, as well as regional ileitis are largely diagnosable by skillful radiological investigation. Much remains to be done before strict methods and interpretations evolve. For that reason, Golden's work is particularly pleasing in that it avoids false claims and merely presents what is known about X-ray knowledge of the small intestine. Undoubtedly, X-ray studies in this section of the gastrointestinal tract are extremely exacting and only the expert can, as

yet, feel at all sure of his results. Nevertheless, the data are so clearly presented that it seems worth while for anyone attempting X-ray work to study the passage of barium through the coils of the ileum fluoroscopically and by serial films during the hours immediately following the ingestion of the meal. For a knowledge of how to proceed, the book should be consulted. Gradually the radiologist may come to feel at home doing this work,—and these studies ought to be made in all cases where the studies of the stomach, duodenum and colon fail to explain the symptoms. The section on the Miller-Abbott tube in the diagnosis and treatment of ileus is especially valuable. While encyclopedic in its approach, the book is terse in its presentation and profusely illustrated. No one attempting serious X-ray studies of the digestive tract should hesitate to buy the book.

ERROR

"The price of Dr. Otto Saphir's 'Outline of Tropical Medicine' is \$1.00 including postage instead of \$2.00 as erroneously stated in a recent issue" . . .

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CLINICAL MEDICINE

STOMACH

OLSON, S. W., AND HECK, F. J.: *Lesions of the gastric mucosa in pernicious anemia.* (Staff Meet Mayo Clinic, v. 20, p. 74, March 7, 1945.)

It was Fenwick in 1877 who first called attention to the pathologic changes in the stomach in cases of pernicious anemia. The weight of early opinion appears to have favored the view that pernicious anemia was a hemolytic anemia due to toxins produced within the digestive tract by bacteria.

Reports have been presented to show that gastroscopically the stomach of the pernicious anemia patient regains its normal appearance after treatment with adequate amounts of liver. At the Mayo Clinic 94 cases of pernicious anemia came to necropsy from 1911 to 1942. Sections of the stomach were examined in 41 of these cases. A large percentage of the sections showed evidence of residual lesions of ulcerative gastritis. Few of the routine sections failed to show acid cells in stomachs obtained in routine necropsies but in stomachs of pernicious anemia patients atrophy of the specialized cells was almost complete. The mucosal

layer in the anemic stomach was thinner than in the non-anemic and there were few glandular tubules. Hyperplasia of the mucous glands was common. The mucosal layer in routine cases was 0.98 mm thick, in untreated pernicious anemia 0.60 mm thick and in treated pernicious anemia 0.85 mm.

The authors emphasize that pernicious anemia is not only a hematologic and neurologic disease but also a disease of the gastric mucosa. Treatment which is sufficient to bring the blood picture back to normal is not always sufficient to prevent atrophic changes in the gastric mucosa. The mucosa may not only become atrophic but may also produce benign and malignant growths.—F. X. Chockley.

BOWEL

RAO, C. K. BHALE.: *A case of acute pain in the abdomen.* (The Antisepsic, v. 40, 6, 519, p. 943.)

The case history is presented of a young man with symptoms of acute pain in the abdomen and history of sudden onset of vomiting and passage of stool. The only interest in the case is that it eventually proved to

be one of malaria with unusual symptomatology at onset.—M. H. F. Friedman.

JOHNSON, B.: *Appendicitis in relation to pregnancy.* (*Med. J. Australia*, v. 2, p. 379, Oct., 1944.)

Appendicitis occurs in women at a rate which is not influenced by a state of pregnancy. Acute attacks occur less commonly during pregnancy, but when they do occur they lead to rapid perforation, frequently within only a few hours. The further advanced the pregnancy the more difficult is the diagnosis of acute appendicitis and the more dangerous the sequelae. Operation should be performed if diagnosis is uncertain and the patient's condition is serious. The incidence of abortion is low if the appendix is intact but if the appendix has ruptured the incidence may be 50 per cent. In simple acute appendicitis during pregnancy the mortality rate is low if operation is performed at once but if rupture has occurred about half of the cases succumb. Perforation is very dangerous to both mother and child during the last two gestation months. The operation of choice is cesarean section followed by appendectomy. The author advocates the removal of a diseased appendix in women who may be expected to become pregnant at some later time.—G. N. N. Smith.

KULIAN, S. T. AND INGELFINGER, F. J.: *Nutritional problems presented by a patient with extensive jejunocolitis.* (*Arch. Int. Med.*, v. 73, p. 466, 1944).

A patient is presented who had an extensive granulomatous jejunocolitis. In addition it was found that the patient suffered a deficiency in pancreatic amylase. Amino acid mixtures were given orally and parenterally to raise the level of plasma proteins. However, the authors found that the patient derived the greatest benefit from orally administered amylase. This is interpreted as being due to increased carbohydrate absorption with a consequent sparing effect on the protein.

PANCREAS

PINKHAM, R. O.: *Pancreatic collection (Pseudocysts) following pancreatitis and pancreatic necrosis.* (*Surg. Gynecol. Obstet.*, v. 80, p. 225, Feb., 1945).

The pseudocysts of the pancreas are usually in one of three sites: 1) between stomach and transverse colon, 2) between stomach and liver, 3) between the leaves of the transverse mesocolon. Other locations as a result of spread and dissection are possible. Cysts may be formed by trauma, acute and chronic pancreatitis, and hemorrhagic necrosis. The wall of the pseudocyst is formed of connective tissue whereas a true cyst has an epithelial lining. However, this may not be distinguishable.

Differentiation of pancreatic cysts from suppurations is often difficult. Suppuration is probably a superimposed infection on a pancreatic cyst. The contents may be blood, clear fluid, necrotic tissue, trypsin, amylase, lipase, and bacteria. Suggestions are offered for classifying pancreatic collections as to etiology:

trauma, inflammation, necrosis, retention and true cysts (neoplastic and congenital).

Six cases are reported in which the cyst was secondary to acute pancreatitis. There were two cases each of collections found subsequent to suppurative pancreatitis and chronic pancreatitis. There was no relation between serum amylase and the amylase of the cysts.

Diagnosis of pancreatic cyst is obscure inasmuch as history may simulate any upper abdominal disease either acute or chronic. Pain may be absent. Hemorrhage into the cyst is evidenced by nausea, vomiting and pain. Since biliary tract disease is often associated with pancreatic collections, this is a matter of added confusion. Roentgenography including pneumo-gastrograms is a valuable adjunct. Serum amylase determinations are most important, particularly if there is persistent elevation. Treatment consisted of drainage or marsupialization of the collection.—Wm. J. Snape.

SARIEPY, L. J.: *Acute hemorrhagic pancreatitis: case report.* (*West. J. Surg. Obstet. Gynecol.*, v. 53, p. 45, Feb., 1945).

Diagnosis of acute hemorrhagic pancreatitis is difficult principally because of its infrequency and the easy confusion with other conditions. Symptoms are generally not characteristic. A case is reported of a 37 year old female complaining of pain. The pain at first was generalized, then it was localized to the epigastrium and was associated with pain in left shoulder. She appeared cyanotic and moderately distended but not rigid. The temperature, pulse and respiration were within normal limits. Scout film showed many small gallstones. Cholecystotomy was done. She survived 6 days. Post mortem examination showed usual findings.—Wm. J. Snape.

JALESKI, T. C.: *Pancreatic lithiasis.* (*Ann. Intern. Med.*, v. 20, p. 940, 1944).

The author reports two cases. These patients presented the syndrome of upper abdominal pain crisis. Pancreatic calculi could be visualized readily. There was steatorrhea and both the external pancreatic secretion and the blood sugar curves were disturbed. A total of 220 cases have been reported in the literature to date, 118 of these during the past twenty years.—Wm. J. Snape.

LIVER AND GALL BLADDER

MACDONALD, R. M.: *Toxic hepatitis in fever therapy.* (*Canadian Med. Assoc. J.*, v. 51, p. 445, Nov., 1944).

Fever therapy rarely results in jaundice as one of its complications. However, MacDonald finds that artificial fever will result in toxic hepatitis if the patient has a relatively high blood level of one of the sulfonamide drugs. In 250 men with gonorrhea who received sulfonamides and high fever therapy, the incidence of jaundice was 19.2 per cent (48 cases).—D. A. Woerner.

ABSTRACTS

WEEMS, H. S.: Cholelithiasis—sickle cell anemia. (*Ann. Intern. Med.*, v. 22, p. 182, Feb., 1945).

Although biliary colic and gallstones have at times been mentioned in the literature in connection with sickle cell anemia, reference to this association is not made in most commonly used text books. Four cases are reported here. One patient was a 13 year old male and one was a 24 year old female with cholelithiasis and symptoms of possible biliary dyskinesia, a third was a 35 year old male with a probably non-functioning gall bladder and symptoms, and the fourth was a 38 year old male with silent cholelithiasis. All patients were colored. They had definitely proved sickle cell anemia. Twelve of 44 necropsy reports of sickle cell anemia available showed gall stones either present, or to have been surgically removed previously. They were observed in the second, and commonly in the third and fourth decades. Eight of the 12 were males. Although figures are at considerable variance, it is quite definite that the normal incidence of gallstones is much lower than this in the negro. It is not believed that the crises of sickle cell anemia can be explained solely on the basis of biliary colic, since the crises have continued in some patients after cholecystectomy. However, the presence of biliary calculi in the young negro calls for careful evaluation and search for sickle cells.—Wm. D. Beamer.

MCGARTY, M. A.: Jaundice and its surgical aspects. (*Wisconsin Med. J.*, v. 43, p. 1043, Oct., 1944).

Mortality rates following operation on the biliary system have been reduced in the past fifty years from 16 per cent to less than 3 per cent. Primarily this is due to our increased knowledge of the physiology of the liver and biliary system. Improved anesthesia methods, surgical techniques, gastric suction and intravenous medication have been largely contributory to the good results. Administration of vitamins B and C and the fat-soluble vitamins A, D and K have also been responsible. The liver should be protected by a high carbohydrate diet, supplemented by intravenous dextrose if necessary. Meat protein should be kept at a minimum in the diet. Bile salts are given to assist in absorption of fat-soluble vitamins.

Of great importance is the use of dextrose in pre- and post-operative care, especially in the presence of hepatic insufficiency. Prothrombin clotting time should be determined in all cases with evidence of jaundice. Vitamin K should be given preoperatively to prevent excessive bleeding. Bile salts should also be included. The author mentions the use of oxalic acid to check hemorrhage.—F. X. Chockley.

KERN, R. A. AND NORRIS, R. F.: Liver involvement in malaria. (*U. S. Naval Med. Bull.*, v. 43, p. 847, Nov., 1944).

Observations were made on 1153 patients with malaria. The frequency of liver involvement was high. In 100 consecutive cases of proved malaria the liver was found to be enlarged in 59 cases. Enlargement of liver and spleen followed the course of the disease. The liver enlarged with the beginning of fever and grew

smaller as the fever subsided. Tenderness of the liver was noted in 8 of the 59 cases with enlarged livers. Altho there was concomitant impaired liver function the disease did not reach the stage of jaundice. In some cases hepatic abscesses were suspected.

The nature of the changes in the liver which result in the enlargement is not clear. Apparently the parenchymal cells swell and compress the sinusoids. Malarial pigment is found in the Kupffer cells. In order that the liver may be spared as much as possible the diets recommended should be low in fat but high in carbohydrate and protein.—I. M. Theone.

ULCER

TIDMARSH, C. J.: Medical treatment of ulcer hemorrhage. (*Canad. Med. Assoc. J.*, v. 52, p. 21, Jan., 1945).

Until recently the treatment of the bleeding ulcer patient left much to be desired. Probably only about twenty per cent of hemorrhagic ulcer cases come to the hospital so that true evaluations are not possible. Most patients showing active bleeding are in their fourth and fifth decades. This may mean that the ulcer has been present for some time but awaited proper conditions for hemorrhaging. Also this perhaps points up the relationship between arteriosclerosis and bleeding ulcer, the two occurring in the same patients quite frequently. Younger patients of course may, and do, also have bleeding ulcers but these usually are acute and occur with short ulcer histories. Prior to the Mulengracht prompt feeding regimen the mortality rates varied from 8.7 to 25 per cent; now the mortality rate is less than 2 per cent. Not only is the ulcer better managed but the patients' morale is improved. The Mulengracht regimen has not been maintained in this country in its original form. It has been modified by several clinicians in some details, mainly minor. Morphine and opiates produce intestinal spasm and are avoided; instead atropine and one of the barbiturates are used. Shock, if present, must be attended to immediately by prompt blood transfusion. The patient must be carefully studied and observed throughout the treatment period. If bleeding continues surgery must be employed. However, surgery should be considered only in selected cases, with special attention being paid to age, history and clinical findings.—D. A. Wocker.

MORRIS, J. N. AND TITMUS, R. M.: Epidemiology of peptic ulcer vital statistics. (*Lancet*, v. 2, p. 841, 1944).

In England and Wales during the last ten years there were 43,000 deaths registered as being due to peptic ulcer. This is little less than one per cent of the non-violent death rate. The death rate in men over 45 years is rising significantly but it is falling in women. Gastric ulcer in both sexes is more fatal than duodenal ulcer. In men under 55 years of age the mortality from stomach ulcers is related in some manner to the patients' economic level but no such relationship exists for duodenal ulcer deaths. In older men death from either gastric or duodenal ulcer is definitely more frequent in the economically better classes. The death rate

from ulcers in urban areas is higher than in rural areas. Ulcer mortalities increased sharply during the depression periods of the 1930's and during the heavy air attacks early in this war.—F. E. St. George.

THERAPEUTICS

PATERSON, D., PIERCE, M. AND PECK, E.: *The treatment of coeliac disease with vitamin B complex and concentrated liver.* (Arch. Dis. Child., v. 19, p. 99, 1944).

Twenty-six cases of idiopathic coeliac disease and four cases of "coeliac syndrome" were studied. The patients were treated with parenterally administered concentrated liver extracts and with both oral and parenteral vitamin B complex preparations. When the dosages of the drugs were sufficient and administered often there was a good gain in both weight and height. The general health showed marked improvement. Best results were obtained when the vitamin B complex was given parenterally rather than orally in conjunction with the liver concentrates. In 18 out of twenty-six cases the stool fat content decreased to normal ranges and in the other cases there was evident improvement. Presence of upper respiratory tract infections decreased the rate of improvement. Vitamin A absorption curves were not improved by the treatment while oral glucose tolerance curves returned to normal in some cases.—G. Klenner.

REHFUSS, M. E.: *The medical treatment of gall-bladder disease.* (J. Med. Soc. New Jersey, v. 41, p. 431, Dec., 1944).

In gall bladder disease 90 per cent of the patients complain of flatulence and upper abdominal indigestion; 71 per cent have distress, 76 per cent experience pain, 51 per cent show dizziness, 40 per cent show cardiovascular phenomena and 32 per cent have rheumatic symptoms. Eradication of infection of any kind is the first step in treatment. Sulfonamides have been successful. Rest and rigid diet are essential. Menthenamin, salicylates and alkalinization have proved disappointing tho some clinicians still endorse them. Duodenal drainage may bring relief but should not be tried in severe gall bladder disturbances. Antispasmodics, adsorbents, sedatives and regulation of bowel habits are essential. Moist heat, bismuth subcarbonate and analgesics are advised for abdominal distress. If medical treatment fails to bring improvement, then some form of biliary surgery must be performed. However, extensive pre- and post-operative care of the patient must be used to make the results successful.—Wm. D. Beamer.

SURGERY

HAND, B. F.: *The role of fluids administered orally in causing postoperative distension following gynecologic operations.* (J. Florida Med. Assoc., v. 30, p. 426, 1944.).

One hundred cases were studied by the author. Those who were given fluids by mouth shortly after the operation tended to develop distension. The degree of distension was greater when the fluid was cold. With-

holding all fluids for 24 hours and then giving hot fluids resulted in few cases of distension. Parenteral administration of 2000 cc. of 5 per cent glucose will usually alleviate the thirst felt after operation. Pitressin or prostigmin are valuable after the first 24 hours but not effective in moving on the gas in the bowel before this.—M. H. F. Friedman.

FISHER, H. C. AND BURCH, J. C.: *The treatment of acute appendicitis.* (Southern Med. J., v. 38, p. 255, Apr., 1945).

The most common surgical disease of the abdomen is appendicitis. The mortality rate has been reduced to near the vanishing point. At the Brooke General Hospital, Fort Sam Houston, Texas, there were 1494 appendectomies from September 1940 to July 1944 with only two deaths. More than half of the cases were between 21 and 30 years of age. Acute suppurative appendicitis occurred in 718 cases. Of these, 73 cases were perforative with 39 having general peritonitis. Early diagnosis and operation were responsible for the low mortality. Simple acute appendicitis averaged 13 hours in duration before operation while those that perforated went to 83 hours. The McBurney incision was practically routine. Sulfonamides (sulfanilamide mainly) were used whenever there was indication for it. Postoperative wound infections were reduced from 3.4 to 1.1 per cent by employment of cotton as the ligating material. Patients were allowed out of bed to void after the eighth hour and were permitted to walk about for simple duties by the end of the fourth day.—G. N. N. Smith.

WILKINSON, A. W.: *Imperforate anus.* (Arch. Dis. Child., v. 19, p. 138, 1944).

The method of treatment and the prognosis in cases of imperforate anus are determined largely by the level at which the rectal obstruction or blind end of the rectum occurs. A membranous obstruction is easily diagnosed. But when the blind end of the rectum ends high up the accumulated meconium does not bulge out and intestinal obstruction is truly complete. If the end of the stump is low, it may be pulled down and proctoplasty attempted. But if the end of the rectal stump is high this procedure is dangerous and should be replaced by colostomy. The author recommends blind puncture of the rectum and aspiration of the meconium with a wide bore needle. He has found that radiologic evidence of absence of gas does not necessarily mean absence of a rectal stump which may be sufficiently low for proctoplasty operation.—I. M. Theone.

GLASSER, S. T.: *Surgical considerations in the modifications of gut rotation.* (Bull. New York Med. Coll., v. 7, p. 74, Dec., 1944).

Surgical considerations in the modification of gut rotation are presented. The actual number of individuals with malrotated intestines is higher than shown by records because the anomalies may be considered minor when discovered and not be recorded. Most patients with errors in rotation of the gut experience no pain or have no reason to suspect their condition. The sex

incidence is about 2 men for each woman. The importance of the malrotated gut lies mainly in the nature of the abdominal symptoms which an individual with an anomaly will present when there is intestinal pathology. The possibility of these anomalies in gut rotation should always be kept in mind, particularly when intestinal obstruction or inflammatory lesions are considered in the adult or differential diagnosis of intestinal conditions are considered in the infant. It is desirable that the surgeon be familiar with the main types of embryologic anomalies he may encounter. Glasser presents a few hints and guides to assist the operating surgeon.—H. Stilyung.

EXPERIMENTAL MEDICINE SECRETION

HENDRIX, B. M., CALVIN, D. B. AND GREENBERG, M. M.: *The relation of the excretion of gastric juice and of urine to the alkalosis of hydrazine intoxication in the rabbit.* (*Texas Reports Biol. Med.*, v. 2, p. 259, Fall, 1944).

Hydrazine is a specific liver poison that has been used in certain metabolic studies. Following administration of hydrazine alkalosis develops. The alkalosis appears to be due to loss of chloride by vomiting of gastric juice rather than to the direct action of the drug on the liver.

The present study was undertaken on rabbits because rabbits do not vomit and therefore chloride cannot be lost from the body by this means. It was found that the hydrazine caused an increase in the carbon dioxide capacity of the blood and of the plasma. The increased plasma carbon dioxide capacity is approximately equivalent to the increase in total fixed base of the serum. The ratio of base to chloride is actually increased so that probably the increase in available base is due to increase in free acid secretion in the stomach.—M. H. F. Friedman.

MOTILITY

BLICKE, R. E. AND FELDKAMP, R. F.: *Antispasmodics.* (*J. Am. Chem. Soc.*, v. 66, p. 1087, 1944).

The water soluble hydrochlorides of several synthetic basic esters were studied with respect to their spasmolytic action. The isolated intestine was used as the test organ. Effective relaxation of the intestinal strips was produced in dilutions as high as one part per million to one part per two million when several alpha naphthylethylacetate and alpha naphthylphenylacetate esters were used.

ABSORPTION

EMMEL, V. M.: *Alkaline phosphatase in the Golgi zone of absorbing cells of the small intestine.* (*Anat. Rec.*, v. 91, p. 39, Jan., 1945).

The author used histo-chemical technique in studying the site of formation or activity of alkaline phosphatase. The enzyme was found particularly abundant in the striated cuticular border of the epithelial cells of the small intestine. The enzyme appeared to be in its greatest concentration in the region of the Golgi zone. No other cell types showed this distribution. Phosphorylation is an important step in the absorption of fats and carbohydrates. Since these intestinal cells no doubt

take part in the function of absorption, it is suggested that the Golgi zone in these cells may be important in the passage of these absorbed materials thru the cells.—M. H. F. Friedman.

PATHOLOGY

ENTENMAN, C., CHAIKOFF, I. L., AND MONTGOMERY, M. L.: *The preparation of fractions from pancreas that prevent fatty livers in depancreatized dogs maintained with insulin.* (*J. Biol. Chem.*, v. 155, p. 573, 1944).

A non-dialyzable anti-fatty liver factor, soluble in dilute acid and insoluble in 0.25-0.5 per cent saturated ammonium sulfate solution, was found in the pancreas. Prevention of abnormally fatty livers for 5 months in depancreatized dogs maintained with insulin was taken as evidence for the presence of the factor in the material fed.—Biological Abstracts.

SEIFTER, J.: *Liver injury in dogs exposed to trichloroethylene.* (*J. Indust. Hygen. Toxicol.*, v. 26, p. 250, 1944).

Bromsulfalein and chloral liver function tests were performed on dogs exposed to trichloroethylene vapors. Daily exposure for 7 to 8 hours per day for 3 weeks resulted in liver damage when the concentration of trichloroethylene in the air was 750 parts per million. Exposure for 4 to 6 hours per day, 5 days per week took 8 weeks to produce liver damage when the concentration was reduced to 500 parts per million. Glycogen depletion and hydropic parenchymatous degeneration were found. Liver dysfunction, nausea, vomiting and diarrhea were further evidence of toxicity. Lethargy also developed. Signs of intoxication disappeared rapidly following removal of the dogs from exposure to the trichloroethylene.—I. M. Theone.

KNOCKER, P. AND MANDELSTEIN, J.: *Rhythmic liver changes in the rat produced by a single injection of chloroform.* (*Nature*, v. 154, p. 148, 1944).

The authors describe a rhythmic cycle of liver changes in rats following the injection of sub-lethal doses of chloroform. Similar changes were also found to occur in the guinea pig. The changes consisted of alternate appearance and disappearance of fat within the course of a few days. Binucleated liver cells varied with the fat content. The kidney also showed a similar fat rhythm. The mortality of the chloroform-injected animals was highest during the phase of the cycle that showed the highest concentration of fat in the kidney and liver.—F. E. St. George.

GOULD, B. S.: *The source of serum phosphatase. The nature of the increased phosphatase in rats after fat feeding.* (*Arch. Biochem.*, v. 4, p. 175, 1944).

Rats kept on an exclusive diet of powdered whole milk showed a higher serum phosphatase level than rats kept on a standard mixed animal diet. It was found that the fat in milk was responsible for the increase in serum enzyme concentration and that a similar increase could be produced by feeding fats or fatty acids. It was concluded that while in normal young

animals the serum phosphatase was of osseous origin, in normal adult rats and rats fed fats the serum phosphatase is of intestinal origin.—B. R. Adolph, Jr.

MISCELLANEOUS

EDWARDS, LESLIE E.: *The effect of cocarboxylase on the conversion of fat to carbohydrate.* (Science, v. 100, p. 268, 1944).

Cocarboxylase was injected intravenously into depancreatized dogs the fourth and sixth day after insulin and after complete healing. It increased the sugar excretion. The R. Q. dropped from about 0.70 to 0.59 and even to 0.51 by feeding sodium butyrate to the animal treated with cocarboxylase. The R. Q. drop was caused by a decrease in the CO₂ expired. Sugar excretion in the urine increased. This caused an increase in the D:N ration without a significant change in nitrogen excretion. It indicated conversion of fatty acid to glucose. The course of the conversion was analyzed by showing that pigeon breast muscle oxidized pyruvic acid faster when treated with an extract of rat kidney cortex which had been incubated with sodium acetoacetate than when treated in the same manner without acetate. Diabetic animals fed acetoacetic acid plus cocarboxylase had increased urinary citric acid excretion. Citric acid was converted to glucose only when cocarboxylase was present. Acetoacetic acid passes to citric acid and thence to glucose.

—Courtesy Biological Abstracts.

BRUCH, HILDE.: *Dietary treatment of obesity in childhood.* (J. Am. Dietetic Assoc., v. 20, p. 361-364, 1944).

Experience and careful dietary histories of obese children in clinics emphasized the fact that overeating is a major cause of most obesity. Unwise parents and environment unfavorable to full emotional development are often contributing factors. Mothers of fat children are singularly unable to permit a normal unfolding of their children's potentialities. Well balanced dietaries and frequent clinic visits were successful in reducing weight and often achieved psychiatric success.

—Courtesy Biological Abstracts.

SAWYER, C. H.: *Hydrolysis of choline esterase by liver.* (Science, v. 101, p. 385, Apr. 13, 1945).

An esterase is presented in strong concentration in the liver of the guinea pig and also of the rabbit which splits benzoylcholine but has no effect on acetylcholine hydrolysis. The significance of this is discussed briefly.

PATTERSON, W. H. AND SMITH, G. S.: *Latent mastoiditis in infancy.* (Brit. Med. J., v. 1944, No. 4376, p. 654, 1944).

In 49 children with clinical histories of diarrhea and vomiting, pus was found at necropsy in the mastoid cavities of 35. The post-mortem and bacteriologic findings, as well as the clinical data, do not suggest that mastoiditis is an etiological factor in the gastro-intestinal symptom complex. Mastoid cavities contain-

ing pus were found in about the same high rate in children succumbing to other diseases, such as those of the respiratory system. *Pneumococcus* was the organism isolated most often. Infants under six months of age showed the highest frequency of infected mastoids.—F. E. St. George.

LEA-PLAZA, H., NUÑEZ, R. AND DONOSO, S.: *Anatomico-clinical study on hypovitaminosis B.* (Rev. Med. Chile, v. 72, p. 649-659, 1944).

Four cases of hypovitaminosis B are described, each with symptoms of lack of niacin, including pellagrous erythema and anemia. The symptoms of nervous system involvement were almost entirely ascribable to changes in the central nervous system. Such symptoms were states of delirium, confusion, and frank psychosis; and also pyramidal and extrapyramidal manifestations. Anatomical study of the central nervous system showed demyelination of fibers, hyperchromatism of nerve cells in some portions, dissolution of Nissl substance in others, and definite increase in number of satellite cells. The trunks of the peripheral nerves appeared to be normal. The authors point out that depending on what portion of the complex vitamin B is lacking, the manifestations of deficiency vary. Thus when thiamine is largely lacking the peripheral system is first affected, with a progressive centripetal advance. When as here the PP factor, probably in combination with the B₆ factor (pyridoxine) and the B₂ factor (riboflavine) are lacking, the central nervous system shows the earlier alterations with possibly a slowly progressive centripetal advance. From these observations, some recommendations in regard to treatment are made.—Courtesy Biological Abstracts.

CHAMBERS, R. AND ZWEIFACH, B. W.: *Topography and function of the mesenteric capillary circulation.* (Am. J. Anat., v. 75, p. 173, 1944).

The results presented in this paper offer evidence for the existence, in the capillary bed of the omentum of the dog and the mesoappendix of the rat, of a precise mechanism for conditioning the rate and amount of blood flow through the bed. The relative autonomy of the capillary circulation depends largely on 2 features. One is the highly specific arrangement of the muscular vessels of the capillary bed. The other is the exposed disposition of its muscular elements which, although normally subject to constrictor nerve impulses, readily come under the relaxing influence of local tissue conditions. A new term, metarteriole, is introduced to indicate the discontinuously muscular, proximal portion of the capillary-like central channel which courses through the capillary bed from the terminal arteriole to the beginning venule. The metarteriole and its precapillary offshoots, supplied with sphincters, are highly reactive to constrictor and dilator drugs. Under normal conditions they spontaneously undergo alternating constrictor and dilator phases. This type of movement, termed vasomotion, controls the ischemia and hyperemia of the capillary bed.—Courtesy Biological Abstracts.

Gerontology

By

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THERE have appeared recently some efforts to include Geriatrics as a specialty in medicine, corresponding to Pediatrics; e.g., Meyer Golob's (1) recent article, A. Lambert: (2); J. L. Nasher: (3); M. V. Thewlis: (4); E. V. Cowdry: (5); and others. Cowdry emphasizes that the aged should be treated as individuals, not *en masse*. He also suggests "that the greatest burden is failure to get rid of aged elastic fibres and systematically to replace them with new ones." Golob accentuates that *Gerontology* is the process or condition of growing old, or the science of aging; while Geriatrics concerns itself with diseases peculiar to the aged.

There are some underlying fundamental principles which I wish to present, which form a very important chapter in *Preventive Medicine*. Aging has long been taken for granted, that senescence is all decline and is merely the precursor of senility and death, and that nothing can be done to prevent it.

In 1935 I (6) reviewed the great work of Timothy Leary (7) on the high content of lipoids in atherosomatous aortae. He reproduced the identical lesions in the rabbit by feeding cholesterol—pathologically the same as occur in the coronary arteries of young and old diabetics, as disclosed by autopsies in the Joslin clinic. Leary later reviewed the records of one decade in the clinic of high fat feeding compared with one decade of low fat diet. He revealed a tremendous decrease in coronary disease in the period of low fat dietary. Recently Hirsch and Weinhouse (8) have corroborated Leary's contention that lipid deposition in the intima is the primary lesion in atherosclerosis and that the old view that primary lesions in the *media* resulted in atherosclerosis was incorrect. Leary summarized his views as follows: "All the lesions of aortic atherosclerosis, save the early mucoid change, are due to the presence of cholesterol. In old age cholesterol metabolism ceases, globular lipophages accumulate in masses, with inadequate nutrition and support and a primary atherosomatous 'abscess' is the typical lesion. Atherosclerosis is a disease due to disturbances of the cholesterol metabolism. Stresses appear to be responsible for the localization of the lesions. Advanced atherosclerosis is the result of years of progressive accretion. The fact that the cholesterol content of the blood is low is not evidence that it was not high at times during its development. Thyroid and Iodine are cholesterol solvents." Rabinowitch (9), head of the diabetic clinic in Montreal, confirmed Leary's conclusions. Joslin (10) also is in accord with Leary's clinical view of the subject.

It is clear that blood cholesterol determinations have no place in the diagnosis of cholesterol deposits. These deposits occur not only in arteries, but are responsible

for cataract, degenerative arthritis, gout and gall stones, and in all probability for the loss or degeneration of elastic fibres. We must employ our clinical judgment in estimating the cholesterol metabolism of any individual. The patient with poor cholesterol metabolism is nearly always obese, while some of the thin ones, endowed with good cholesterol metabolism, may live to old age, constantly eating high cholesterol foods.

We are indebted to Bridges (11) for a complete table containing the cholesterol content of practically all food stuffs. Some of his figures are presented revealing the tremendously high content of these foods, viz.,

	Mg. per 100 g.
Egg yolk	2647
Brains	3700
Kidney	3400
Liver	3400
Pancreas	3120
Thymus	2300
Salmon roe	2200
Caviar	295
In contrast:	
Beef contains only	76
Mutton	37
Potatoes	2.6
Spinach	5.5

All fruits and vegetables show small percentage figures.

Cholesterol is present in all foods to a small percentage excepting egg albumin, which contains none. Those foods rich in it are egg yolk, the solid internal organs—liver, sweetbreads, kidney brains etc.

Of course, the child and young adult require a diet of high cholesterol content, but after the age of 35 it should be reduced. I have reviewed old case records in my files and found many histories of patients who have progressively developed obesity, gall stones, atherosclerosis, degenerative arthritis, and cataract.

The aging individual should live on a diet low in cholesterol content. He should avoid the general loss of elastic fibers by regular deep breathing and stretching exercises. He should have definite periods of relaxation and rest—remember the *Law of the Conservation of Energy* applies to living organisms as well as to the field of mechanics. The scalp should not be permitted to adhere to the skull; a few minutes' massage with your own hands daily will prevent it. The "gummy eye" of the aged can easily be prevented by your oculist.

In conclusion, I wish to present the results of my clinical experience during the last ten years with a few illustrative case histories.

1. *Diabetes.* I see many patients who have been under treatment elsewhere with high fat diet and large doses of insulin. After two months or so of low cholesterol diet and the administration of thyroid extract they lose weight, the large liver returns to normal size, the tolerance for carbohydrates improves, much smaller dosage of insulin is required, and they are vastly improved in general health and well-being.

2. *Gall Bladder and Liver Diseases.* Patients with obstructive jaundice due to acute or chronic cholecystitis have made remarkable improvement with low cholesterol diet, the administration of thyroid and a daily early morning dose of magnesium sulphate. Early cases of cirrhosis are much benefitted by this regimen. Bile salts, which are so often prescribed, are contraindicated.

3. *Cardiovascular — Renal Disease.* Patients with arterial hypertension, coronary artery disease, cardiac decomposition, acute and chronic nephritis, cerebral atherosclerosis, and peripheral arterial disease should be limited to a diet of low cholesterol content. One must determine clinically whether iodide or thyroid medication is indicated.

4. *Gout and Degenerative Arthritis.* I have achieved many good results in patients of this character. Dr. J. Albert Key (12) Professor of Orthopedic Surgery in the Washington University School of Medicine, says, "We find that our patients with degenerative arthritis do better than have similar patients in the past under any form of treatment which we have used. We feel that we are able to prevent the progress of the disease in cases in which it is definitely present and to prevent its development in the type of individual in whom it is to be expected."

5. *Cataract.* Patients seen in consultation with ophthalmologists who have kept close observation over them have shown an arrest of the disease in many cases.

6. *Atherosclerotic Ulcer of the Stomach.* The ulcer is usually located on the lesser curvature of the stomach and occurs in elderly individuals. It is possible to outline a low cholesterol smooth diet list which is very effective in the treatment of these patients, as I have detailed in my book on *Clinical Gastro-Enterology*. (13)

Case No. 1

Male, aged 61, height 6 feet, weight 200 pounds, blood pressure 180/100.

Gall stone operation July 15, 1929 by Dr. Evarts A. Graham. Good recovery. He was now put on a diet of low cholesterol content and given two grains of desiccated thyroid daily, regardless of a normal basal metabolism rate; subsequent EKG's disclosed definite improvement. He continued to improve until in September 1943, when he made a business trip and could not follow his usual regimen; upon his return home he had an attack of nausea and became jaundiced. On October 6, 1943, I saw him in consultation with Dr. Samuel B. Gran and Dr. Evarts A. Graham. His liver was enlarged three fingers' breadth below the rib margins. The bile salts which he was taking was discontinued and he was fed fruit juices and gelatinous every two hours. Brewers' yeast powder and desiccated thyroid were given once daily and saturated solution of magnesia sulphate was given every morning on fasting stomach. His recovery was rapid. In two weeks time the liver was no longer palpable, the jaundice and nausea dis-

peared, and he has remained in good health since, on his former regimen of thyroid, yeast powder, and low cholesterol content diet list, deep breathing and stretching exercises.

Case No. 2

Male, aged 51, height 5 feet, 6 inches, weight 195 pounds. Came under my observation in January 1937.

He had been under treatment elsewhere for seven years for diabetes. He was on high fat diet and was taking 60 units of insulin daily. Physical examination revealed a dry skin, obesity and a very large liver—a hand's breadth below the rib margins—blunt, smooth edge. Blood pressure 200/110. Basal rate +8. He was put on low cholesterol diet list with the administration of Gr. II desiccated thyroid once daily on fasting stomach. His chief complaints were headache, vertigo and dyspnoea on exertion. Heart normal in size, no murmurs. EKG revealed no myocardial or coronary pathology. He made quite a rapid improvement. The liver no longer palpable after two months' time, blood pressure reduced to 150/90, weight reduced to 150 pounds. He was subjectively much improved and his carbohydrate tolerance was increased and only twenty units of insulin were required daily.

Case No. 3

Female, aged 63, height 5 feet, 6 inches, weight 140 pounds, came under my observation September 3, 1938.

Chief complaints were pain in back and knee joints, vertigo, diarrhea, belching gas and bloating in abdomen. Physical examination revealed no lesions in heart or lungs. Abdominal muscles were relaxed, pelvic organs normal, palpable arteries hard. Blood pressure 190/100. X-ray of chest revealed rather wide aortic arcus. X-ray of gastro-intestinal tract was negative, except a very spastic iliac and pelvic colon. X-ray of the back and knees showed deposits in the lumbar vertebrae and edges of femur and tibia. EKG, blood sugar and NPN were all within the normal limits. Fractional stomach content analysis disclosed *achylia gastrica*. No free HCL in any specimen, highest total 10. Feces analysis showed considerable excess of mucus and many *trichomonas hominis* and striated muscle fibers. Blood: serological negative, a mild degree of secondary anemia, no trace of the pernicious type. Basal metabolism rate +15. Procto sigmoidoscopy, 10-inch view, revealed sphincter spasm, strong contracture at recto-sigmoid region. The mucosa of both rectum and sigmoid was deeply congested with absence of superficial veins, and covered with many small clumps of mucus, no ulcerative process.

Final diagnosis. *Degenerative arthritis, atherosclerosis, hypertension, achylia gastrica, cataract, colitis, trichomonas hominis infestation.*

Treatment. Stovarsol tablets .25 gm. one t.i.d. before meals for one week's time eliminated the trichomonas. Low smooth cholesterol diet. Thirty minims of dilute HCL t.i.d. in fat-free Bulgarian culture milk to which was added one heaping teaspoonful of Squibb's Brewers' Yeast Powder, and twenty minims of saturated solution of sodium iodide. In two months' time the diarrhea ceased, the stools became normal, the blood pressure was 150/80, there was much less back pain and stiffness in the joints. She comes for an annual check-up and I saw her in December 1944. Blood pressure was then 140/80. She was free from all discomfort. She was still taking HCL, iodide and yeast in Bulgarian fat-free milk, adhering to her diet list, and taking deep breathing and stretching exercises.

Case No. 4

Male, aged 73, height 5 feet, 9 inches, weight 160 pounds, physician, a devotee of physical exercises who had enjoyed good health. He had had no serious illness. His eyes were myopic and he had worn glasses since the age of twenty years; finally bifocal lenses at the age of fifty. All his life he had mild attacks of heart palpitation which were diagnosed as *tachycardia*. EKG, blood sugar and NPN were all within the normal limits. X-ray of the chest and gastro-intestinal tract revealed no pathology. Basal rate +4. Prostate gland somewhat enlarged. Nocturia one time. No symptoms of bladder blocking and no retention.

Consultation with Dr. Adolph C. Lange revealed a definite arrest of cataract. The clinical record is as follows:

February 0, 1940 first seen: Very early cataracts, central nuclear.
 Mf: OD-5.75-0.75 x 135 = 20/40
 OS-3.25-0.12 x 100 = 20/20

May 20, 1941:
 Mf: OD-6.00-1.00 x 130 = 20/40
 OS-3.25-0.25 x 100 = 20/20

No change in left eye. Only slight increase in myopia of right eye. Objectively cataracts have not increased.

August 29, 1941.
 Mf: OD-5.60-1.00 x 130 = 20/40
 OS-3.75-0.25 x 100 = 20/20

Increase in myopia in both eyes. Vision can be brought up to former level.

April 28, 1942:
 Mf: OD-6.50-1.00 x 130 = 20/40
 OS-4.25 = 20/25

Slight further increase in myopia of left eye.

September 22, 1941:
 Mf: OD-7.00-1.00 x 130 = 20/40
 OS-4.75 = 20/30

Cataractous change has caused an increase in myopia from -5.75 to -7.00 in the right eye and from -3.25 to -4.75 in the left eye. Vision has been gradually reduced from 20/20 to 20/30 in the left eye but in the right eye has remained at 20/40.

Treatment consisted of a diet of low cholesterol content and the administration of twenty minimis of Lugol's solution in grape juice once daily.

Finally, all physicians, not only the Internist, should practice *Preventive Medicine*. They should learn to think in terms of diet, mode of life, physical and mental exercises, correction of bad habits, periods of rest, etc.; i.e., become Fundamentalists instead of merely prescribing relief for present symptoms. Somewhat over a decade of clinical experience confirms the soundness of the theory that cholesterol deposits are responsible for the tissue changes that result in senility. We are able to prolong life, as well as prevent the infirmities due to senescence.

REFERENCES

1. Meyer, Golob: Reflections on Geriatrics in Internal Medicine. *The Am. Journal of Digestive Diseases*: Vol. XI, No. 5, p. 159.
2. A. Lambert: Pharmacology in Old Age. N. Y. Academy of Medicine, (Nov.) 1928.
3. J. L. Nasher: Geriatrics, Second Edition, Philadelphia, 1916.
4. M. V. Thewlis: Geriatrics. St. Louis, 1919. The C. V. Mosby Company.
5. E. V. Cowdry: The Physician's Opportunity to Keep Older People. *Journal A.M.A.* June 10, 1944, p. 402.
6. Horace W. Soper: Cholesterol. *Am. Journal of Digestive Diseases and Nutrition*. August 1935.
7. Timothy Leary: Experimental Atherosclerosis in the Rabbit Compared with Human Coronary Atherosclerosis. *Arch. Path.* 17:453. April 1934.
8. Hirsch and Weinhouse, Sidney: The Role of the Lipids in Atherosclerosis. *Physiol. Rev.* 29:185, July 1943.
9. Rabinowitch, I. M.: Atherosclerosis in Diabetes. *Ann. Int. Med.* 8:1463, May 1935.
10. Joslin, E. P.: Fat and the Diabetic. *New England J. Med.* 209:519, Sept. 14, 1933.
11. Bridges, Milton A.: Food and Beverage Analysis. Lea and Febiger, 1935.
12. Key, J. Albert, Rosenfeld, Herman Tjoflat, D. E.: "Diagnosis and Treatment of Hypertrophic Arthritis," *J. Missouri State Medical Association*, 159-163 (May) 1938.
13. Soper, Horace W.: "Clinical Gastro-Enterology," The C. V. Mosby Co., 1939, p. 94.

The Newly Isolated Active Principles of Senna. A Preliminary Report

By

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SENNA is a drug of great antiquity and one of our most dependable laxatives of vegetable origin. It is official in the U. S. Pharmacopeia as the leaves of *Cassia acutifolia* or *Cassia angustifolia* and in addition to the crude drug both the fluid extract and syrup are available.

The well known variability in potency of senna and its preparations as well as the side effects of nausea, vomiting and cramping have long discouraged the medical profession in its use. Nevertheless, it is widely employed in domestic medicine in various forms, particularly as an infusion known as 'senna tea'.

Studies into the chemistry of senna by Stoll, Kussmaul and Becker have resulted in the isolation of its various principles some of which, such as emodin, have long been known while others are new. The most

interesting of the newly discovered substances are two specific glycosides known as sennosides A and B. These substances are isomeric and have the same empiric formula, $C_{20}H_{28}O_9$. Both appear as sparkling light yellow crystals with characteristic physico-chemical constants. A fact of especial interest is that hydrolysis cleaves the two glycosides (B easier than A) into aglycones in the molecular proportion of 1:1 and oxidation of both aglycones leads to the anthraquinones known as Rhein.

Pharmacologic investigations by Straub and his collaborators show that the combined sennosides and particularly the A fraction, produce the desirable laxative effect of senna. Emodin which occurs free in the leaves apparently is responsible for much of the cramping and griping side effect. It sets up strong peristaltic waves that follow each other at such short intervals as to resemble spasm and has but a short period of latency between its administration and onset of action. A

smooth increase in colonic motility with just the right degree of laxative effect is only possible with emodin when it is given very slowly. Effective doses cause cessation or lessening of the pendular movement of the small bowel no matter how they are given. Emodin is, therefore, not to be considered as having therapeutic value.

Sennoside A hydrolysis acts very slowly and has the longest period of latency whereas sennoside B is more readily broken up and stands between emodin and sennoside A in its speed action. Sennoside A has no effect on the pendular movement of the small intestine. Emodin has the greatest effect. Here sennoside B is nearer to emodin. This glycoside separates into its aglycone and sugar much quicker than the A glycoside. The sugar radical of both sennosides A and B causes their easy solubility and thus favors their absorption.

Careful studies in the cat by Straub and Triendl have shown that after the oral administration of senna glycosides about six hours is required for them to be effective. When injected intramuscularly the period of latency is approximately five hours and after intravenous dosage it is only one hour. From the time required for the drug to act following the different dosage methods it can be concluded that the longer period of latency following oral administration is due to the time needed for its absorption from the small intestine. Experimental observations on closed loops of intestine show that the sennosides are absorbed from the small bowel and the fact that they are active following parenteral administration indicates that they are carried to the colon by the blood.

The laxative effect of the sennosides results from increased peristaltic action in the colon and two theories have been developed to explain this action. Lenz believes that they directly cause increased irritability of the tissues of the colon whereas Straub localizes the primary effect to Auerbach's plexus from which motility of the colon is stimulated secondarily.

When employed clinically the sennoside complex has a latency period of 10 to 12 hours and it can therefore be administered most conveniently at night with the expectation that it will be effective the next morning. When the dosage is suited to the need of the patient Straub et al., have demonstrated that action of the sennoside complex closely simulates the normal physiological process involved in defecation and that there is no disturbance of water metabolism in the large bowel. From these characteristics it is evident that the desirable laxative effects of senna are due largely to its glycosides. These substances are active both orally and parenterally but so far we have observed only the effects of dosage by mouth. For study purposes a preparation of the sennosides A and B, known as Glysenid was furnished to us* and each tablet was said to contain 12 mg. of the glycosidal complex.

The stimulating action of Glysenid on colonic peristalsis makes it a logical remedy in atonic constipation. Further, its long period of latency as well as its gentle

action can be utilized in proper habit formation to overcome constipation resulting from prolonged neglect of normal rectal reflexes. For this purpose Glysenid can be given after the evening meal to initiate a bowel movement the next morning and as the matinal habit develops the drug can be gradually withdrawn until eventually it is no longer needed. Kottman has reported extensively on this method of treating habitual constipation and regards it as highly successful.

This report covers the use of Glysenid in 156 dispensary and hospital patients (96 females and 60 males). All were over 65 years of age. The dosage employed was one to four tablets depending upon the apparent need and previous history of the patient. In 139 patients the effects were good and without unpleasant side symptoms such as nausea or cramps. An additional 12 patients showed good effects but of these 8 experienced slight cramping and 4 had severe cramps. There were no effects in five.

One tablet proved adequate for 110 patients, while two were needed by 30, three by 11 and four by 5. Female patients responded more readily to the drug, 85% requiring only one tablet, while this dose was satisfactory for only 60% of males. On the other hand 43% of male patients required two or more tablets while only 23% of females needed this dosage.

CONCLUSION

The active principles of senna leaves have been isolated and identified as a complex of two specific glycosides that have been named sennosides A and B.

Clinical observations on 156 patients reported herein show that the sennoside complex is a valuable adjunct in the treatment of constipation resulting from colonic atonieity or from habitual neglect of the impulses set up as a part of the normal defecation reflex.

BIBLIOGRAPHY

- Bethca, O. W.: J. A. M. A. 107: 1298 (October 17, 1936).
- Boekus, H. L., Willard, J. H., and Bank, J.: J. A. M. A. 101: 1 (July 1, 1933).
- Cushny, A. R.: Pharmacology and Therapeutics, 12th ed., Phila., Lea & Febiger, (1940).
- Geiger, E.: J. Am. Pharm. A. 29: 148 (April, 1940).
- Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, Macmillan Co., (1941).
- Kottman, K.: Habitual Constipation and a New Remedy to Improve Defecation, Schweiz. med. Wochenschr. 20: 71 (September, 1941).
- Lenz, E.: Movements of Intestines, Schweiz. med. Wochenschr. 53: 887-893 (Sept. 20, 1923).
- Okada, T.: The Mechanism of the Laxative Effect of Senna, Tohoku J. Exper. Med. 38: 33-44 (March 31, 1940).
- Soilmann, T.: A Manual Pharmacology, 5th ed., Phila. and London, W. B. Saunders Co., (1936).
- Stoll, A., Kussmaul, W. and Becker, B.: The Active Principles of Senna, Verhandl. d. Schweiz. Naturforscl. Gesellsch.: 235-236 (1941).
- Straub, W. and Bergmann, F. V.: Experiments to Determine the Value of Senna Leaves, Arch. f. Exper. Path. U. Pharmacol. 183: 697-699 (December, 1936).
- Straub, W. and Triendl, E.: Theory of the Laxative Effect of Senna and Its Active Principles, Arch. f. Exper. Path. U. Pharmacol. 185: 1-19 (March, 1937).
- Straub, W. and Gebhardt, H.: The Active Ingredients of Senna Leaves, Arch. f. Exper. Path. P. Pharmacol. 181: 399-407, (1936).

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Splenic Abscess. Three Cases of Pyogenic Infection

By

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ENLARGEMENTS of the spleen are easily diagnosed. The palpability of the spleen below the costal margin means it to be at least twice the normal size and, as is well known, several times this increase is not uncommonly encountered clinically. In the presence of marked enlargements thoughts are usually directed to disorders of lipid metabolism (Gaucher disease, Xanthomatosis, Niemann-Picks disease and Schuller-Christian syndrome), to the blood dyscrasias (erythroblastic anemia, "splenic" anemia, congenital hemolytic anemia, myelogenous leukemia), or to tuberculosis, syphilis, chronic septic splenomegaly, cysts, etc. Even isolated or solitary splenic abscess often escapes clinical diagnosis and commonly are temporized with under some diagnosis other than abscess to explain the splenomegaly.

The spleen enlarges readily to a number of conditions and often secondarily such as is seen in septic hepatic and cardiac disease. In primary splenic disorders usually the greatest enlargements are noted, although in myelogenous leukemia marked enlargements can be present. In enlargements due to abscess not enough attention is paid to the past history of an acute infection of the more common types, even one some years back, and as part of the diagnosis, attention to the possibility of a pyogenic infective process in the spleen should be included. However, acute suppurative splenitis may occur rarely without discoverable cause or by infective extension into the organ or following trauma.

Case No. 1., Mr. O. P., Age 54 years. Bartender. Family and personal history non-significant. Was well up to August 1942 when he developed an ischio-rectal abscess which was incised and followed by a rectal fistula. This was operated upon "in sections" and cured. One year after, developed an abscess in left cheek which after incision drained for "some weeks". During this time had an automobile accident, broke three ribs on left side and one month after felt a lump in the splenic region and had occasional pains. During the past year has been examined by several physicians and pronounced normal "excepting the spleen" and for which he received "injection treatments" and x-rays to the splenic region.

The physical examination disclosed only an obese man with a large, hard, rounded spleen which projected into his abdomen and was judged to be about 16 inch (40 cm) in length from pole to pole. Blood pressure 150-80, urine Sp. Gr. 1025, glucose a trace, indican and uroosein three plus, Wasserman negative. Blood WBC 17,800, total polyp 62, band forms

15, segmented 47, small lymphocytes 37 and monocytes 1. Westergren 51, subsequent blood counts taken over three weeks time five in number ran from 18,200 down to 10,900, the platelet count averaging 250,000. A tuberculin Patch test was positive, temperature records taken for a week showed a high point on two occasions of 100.6 being almost normal or at least not significant of a septic condition. Diagnosis, splenic abscess. At operation the spleen was fixed by adhesions, spleen markedly enlarged, thickened peritoneum, finger boring led into an abscess cavity about 4 inch (cm) in diameter filled with greyish-green pus. After drainage and suture, drainage tubes were introduced, the wound drained for about 12 weeks, and the spleen was no longer palpable and the patient made a satisfactory recovery.

Case 2. Miss M. K., age 37, Dressmaker. The past history was mostly characterized by a series of chest conditions. In this was "pneumonia" at 27 and at 33, several attacks of influenza and three or four "attacks of bronchitis" each year. She had never been strong, took tonics for anemia, laxatives for constipation and she was 19 pounds over standard weight. In the mid-winter of 1941 got pleurisy, discontinued her work and finally went to bed because of "chills, fever and extreme weakness". An empyema established, she was operated upon in March 1941, resection and drainage being done. From this she made a slow recovery and about in July, after being at work six weeks, became pyrexic again and complained of periods of pain in the upper left abdomen and lower chest with occasional difficulties of breathing and vomiting blood on two occasions (the empyema was on the right side). Various diagnoses had been made up to about October of the same year.

Upon examination an enlarged spleen was palpated, the liver apparently being normal. The abdomen was large, flabby and the spleen could readily be felt at least one-half of it being below the costal margin and it felt somewhat nodular and was painful to pressure. A distinct anemia was noticeable. Blood pressure 112-78, urine negative, Wasserman negative and tuberculin Patch test strongly positive. Temperature 99.2, pulse 84, Westergren 56. Blood examination Hb. 68 per cent, R.B.C. 3,200,000, W. B. C. 8,400 differential count essentially normal with distinct iodophilia.

On a suppositional diagnosis of tuberculosis of the spleen the case was observed for five days in the hospital. Here the blood remained about the same in four counts, the temperature curve was diphagic, the highest point being 102.8. Three blood cultures were negative. On returning home a distinct chill took place

followed by a temperature of 104.2 F. The spleen noticeably enlarged and became most tender to pressure and a perisplenic friction rub occurred. The diagnosis was changed to splenic abscess probably in a tubercular spleen and at operation a chronically inflamed spleen with a large superficial abscess under the capsule was disclosed. The spleen was removed and although the tube was removed in the second week the wound drained for five months. Recovery and general improvement was established in about seven months after operation. The organism recovered was staphylococcus albus.

Case 3., N. S., 50 years. Bank clerk. Family history of no moment.

Moderate use of alcohol, and heavy cigarette smoker. Seven months before he had a large carbuncle on back of neck, requiring several incisions and x-ray treatments. Urine was negative for glucose at the time. Takes Brewers yeast steadily. Had indigestion for years consisting of belching and a tendency to loose bowels. Lost 20 lbs. in last ten months, distinct fatigue and unable to work at times. Gonorrhoea 21 years ago. "Distinctly irritable and nervous the past year." For about three months has distress in upper abdomen and "feels a lump which seems to be growing larger". Complains of weakness, slight dyspnea. Said he had black stools for two days about 3 months ago. Apparently anemic.

Physical examination blood pressure 138-92, urine Sp. Gr. 1019, otherwise negative excepting 10 pus cells to field. Sclera congested suggesting marked Vitamin A deficiency. Heart slightly enlarged and aorta moderately widened. Easily palpable enlarged spleen and liver. Spleen uniformly rounded and firm and not noticeably tender on pressure. The blood was suggestive of splenic anemia (Banti's disease) showing a hypochromic anemia (Hb 72, R. B. C. 3,700,000), and leucopenia (W. B. C. 4,200 differential not significant) and a slight jaundice (Icterus index 17) Sedimentation 37 (Landau-Adams).

After a week of preoperative preparation a splenectomy was done and surprisingly showed about seventeen small abscesses on the surface of the organ with

several necrotic areas and considerable perisplenitis. *Staphylococcus albus* was culturized. After a stormy convalescence lasting practically two months recovery finally took place. Examined five months after the operation the liver seemed to have returned to normal.

Comment. The three of these patients presented themselves in the office, all of them being able to go about in sufficiently comfortable ways. All three gave the history of a past infection, running from two years to seven months back. All complained of pain in the upper left abdominal region these coming on in periods lasting several hours and never severe enough to stop the patients from being about or requiring opiates. In this there was a distinctive suggestion in that the average case of splenomegaly for whatever disease, pain in the splenic region is not characteristic or so definite in the history. It is probable that the pain is due to a perisplenitis incident to the inflammation and not to stretching of the capsule. Fluctuation could not be elucidated in any, the spleens being uniformly firm throughout. In but one were the constitutional symptoms of abscess (chills, sweats, diaphasic temperature and septic skin color) present and in that one it was not pronounced. In one the leucocyte counts were suggestive, in another only slightly suspicious but not pronounced enough for definite conclusion of septic infection, and in another the blood count was essentially negative. All were in well built persons in which the general condition of the body was good. Loss of weight was not definite. The sedimentation rate was positive in all three, this proving to be the most outstanding laboratory finding. The diagnosis was made in one case, suspected in the second and requiring operation for confirmation, and in the third splenic abscess was not thought of and was disclosed only at operation for splenectomy.

While these are but three cases they nevertheless suggest that in marked enlargements of the spleen, when there had been an infection not too remote in the past and the blood sedimentation rate is high with or without the constitutional symptoms of an infective process, splenic abscess should be thought of. Diagnostic puncture is a blind and dangerous procedure since it may infect the peritoneum.

The Mechanism of Water Balance in the Bowel, and Its Control

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THE control of water balance of the bowel is an extremely important clinical problem, yet little is known about its mechanism. There are few clinical problems that have such widespread clinical implications as the behavior of water in the intestines. Not only is the whole problem of digestion and assimila-

tion tied up with it, but many functional disorders result from its derangements. The problem of constipation alone affects practically everybody at one time or another. The problem of constipation is essentially a problem of disturbed water balance; yet for the most part the mechanism of water balance of the bowel remains a nebulous physiologic haze.

Examination of the literature reveals surprisingly

little information on this subject. The accounts by Gamble (1) in his syllabus and Peters (2) in his monograph are perhaps the best information on the chemical behavior of the fluids of the digestive tract. Standard text books on physiology and various reviews on water metabolism have inadequate discussions on this subject.

Although the existing information on this subject is incomplete, nevertheless we will attempt to review the literature on the present concepts of water balance in the bowel, to which will be added some clinical observations made at the University of Colorado on a rather extensive series of patients.

It must be obvious that water does not float about the bowel in a haphazard manner, producing a diarrhea one day and a constipation the next for no reason at all. There must be some exact mechanism which operates to control the water content of the bowel.

OUTLINE OF STUDY FOR THE WATER BALANCE OF THE BOWEL

1. Ingested fluids.
 - a. free,
 - b. combined.
2. Digestion, secretion and peristalsis,
3. Water content of blood and tissues,
4. Pathologic states influencing water metabolism of the gut,
 - a. infections,
 - b. toxic states,
 - c. etc.,
5. Bile. Its influence on water metabolism of the bowel,
6. Clinical evidence. Biliary Constipation.
7. Summary.

INGESTED FLUIDS

Water is ingested into the body either as a fluid or in chemical combination with solids from which it must subsequently be liberated by diverse chemical processes.

Plain ingested water does not participate in the body functions or structure except for the first few minutes after swallowing.

Water comprises seventy percent of the body mass, yet plain water would soon leave the body by the simple process of flowing away if it were not held there by something else. That something else which holds the water in the body is a great variety of chemical and physical structures, each identified with the particular structure of the body whose water balance it seeks to maintain.

Water is ingested into the body either in fluid form or in chemical combination with solids where it may be present as water of crystallization, colloidal hydrations, simple solutions, or potential water in carbohydrate molecules awaiting oxidation.

While the water is still in the mouth, it may be ejected easily by voluntary effort. After leaving the

mouth it enters the throat where it may still be ejected from the body by the voluntary act of coughing. However when it leaves the throat by passing the pharynx and enters the esophagus, it has passed from voluntary to involuntary control. From sensory-motor control it has passed to that of the autonomic vegetative nervous system, and thereafter it continues on its way autonomically and automatically by steady progression into the stomach, thence into the intestines. Within the intestines or above, it is joined by additional fluid from the blood stream, which may also leave the gut to re-enter the blood stream. The final disposition of water from the body takes place in four ways, (1) through the skin in the perspiration, (2) in the expired air as volatile moisture, (3) through the kidneys as urine, and (4) as retained water in the stool.

The minimal water requirement per day for the adult is approximately 1400 cc according to Gamble (1) so it is assumed that at least this amount must be ingested daily. However part of this water may be obtained from sources in chemical combination with solids.

An ordinary mixed diet yields chemically from 300 to 350 cc of water daily according to Magnus-Levy (3).

The actual fluid intake is usually considerably in excess of the minimum daily requirement. The optimum fluid intake is about two to four times the minimum requirement. It is usually determined by thirst and is influenced by the type of the diet, atmospheric conditions, type of work, numerous pathologic states of the body, etc. In the case of men doing heavy labor in high air temperatures the daily water expenditure may be enormously increased. Dill (4) studied the daily water loss in men working at the Boulder Dam and he observed daily expenditures of 8 to 10 liters per twenty-four hours.

When no food or drink is taken into the body, starvation and dehydration ensue and the tissues themselves are broken down chemically to liberate water. Under these circumstances, the average adult would exhaust his potential available tissue water in ten days and death would result.

Ingested water finally leaves the body in four ways thus maintaining a constant water balance. Water leaves the body as (1) volatile moisture in expired air, (2) sweat, (3) urine, and (4) feces. Of these, the urine fluid is the most variable in amount depending largely on the daily fluid intake. The insensible water loss (sweat and moisture in expired air) as well as the mineral urine output are interrelated to the surface area of the body, while the water content of the stool is the smallest fraction of the daily excretion.

Rowntree (5) states that the average adult excretes from 60 to 150 cc of water daily in the stool. Adolph (6) states that about 100 cc of water per day is excreted in the stool per day per square meter of body surface on an average mixed diet, which makes his estimate slightly above that of Rowntree's.

DIGESTION, SECRETION AND PERISTALSIS

After ingestion into the stomach, the actual progression of water is determined largely by the functions of digestion, secretion and peristalsis.

Practically all writers agree that little or no water is absorbed in the stomach. The removal of the water from the stomach into the intestines is influenced by the other ingested gastric materials and peristalsis. When water is taken alone it is apt to be advanced into the intestine and then absorbed quickly, whereas if taken with food it becomes mixed with other gastric contents and advances slower being dependent upon the gastric peristalsis for its removal into the intestine. Gastric peristaltic waves occur at twenty second intervals. The usual time allowed for normal gastric emptying time is six hours. Actually there is considerable variation in emptying time. It ranges from four and one-half hours in the person of sthenic habitus to six and one-half hours in persons of the asthenic habitus.

Interestingly enough that although little water is absorbed from the stomach considerable may be secreted into it by the blood stream. As much as 2500 cc of fluid may be secreted into the stomach daily in addition to about 1500 cc of saliva much of which is swallowed to join the gastric contents.

The purpose of the gastric fluids is to assist in the process of digestion by converting the solid and semi-solid material into a chyme consisting of solutions and suspensions of partially digested materials, suitable for passage into the small bowel.

In the small bowel the process of digestion and assimilation undergoes a marked speeding up process. Here the peristaltic waves change their character from a slow deep undulating form as seen in stomach to a short quick chopping type having a to and fro motion producing the "feathery" appearance as seen under the fluoroscope. In the jejunum the peristaltic waves occur at two second intervals. In the ileum they occur at five second intervals. The average meal will traverse the entire small intestine in about three hours to arrive at the ileocaecal junction. However it does not immediately enter the colon. Instead a nerve block at the ileocaecal junction arrests its progress for one hour or more, during which time assimilation proceeds. This nerve block area which halts and rearranges the intestinal traffic not only causes a marked delay but also radically changes the subsequent rate of travel. From a short chopping to and fro motion occurring at five second intervals, the peristaltic waves are changed to extremely slow waves which occur at approximately six hour intervals and are of the massive peristaltic type. In the small intestine the bulk of digestion and assimilation takes place. In the small intestine, the assimilation of both food and water proceeds simultaneously. It has been demonstrated experimentally that water is usually absorbed as a solution whose osmotic pressure is nearly equal to that of blood serum. If the intestinal chyme is received from the stomach in a solution more concentrated than the equivalent osmotic pressure of the

blood, then water is secreted from the blood stream into the bowel to dilute it, whereas if the solution is too dilute, then solutes pass from the blood plasma into the fluid to raise osmotic pressure to blood serum level, after which it is absorbed into the blood stream. The small intestine normally secretes about 3000 cc of fluid daily in addition to about 750 cc of bile and an equal amount of pancreatic juice which it receives from these organs. Most of this fluid is shortly reabsorbed into the blood when the intestinal chyme has been reduced to the blood osmotic pressure. Interestingly enough it appears that about 8500 cc of fluid is thus secreted by the digestive apparatus daily, although the total blood stream plasma is only 3500 cc.

In the colon assimilation is completed and waste material removed from the body. The intestinal chyme poured into the colon is homogeneous in character on gross appearance and semi-fluid in consistency. It is from this material that the stool is formed. At this stage the chyme represents the crude waste material from the small intestine which will undergo further refinement to prepare it for ultimate ejection.

The colon really has two separate and distinct functions, and these are identified with the two sides of the colon. The right side completes the process of digestion and assimilation while the left side ejects the final waste material from the body. The right side of the colon removes much of the water from the chyme also some of the salts, some of the simple sugars and some amino acids. By this process the chyme is changed from a liquid material to a soft putty like mass which is then advanced by the massive peristalsis occurring approximately every six hours to the left side of the colon where it will be expelled from the body once daily. The normal number of evacuations however varies from twice daily in the persons of the sthenic habitus to once in two days in persons of the asthenic habitus.

As stated the condition of blood plasma osmotic pressure of the bowel contents favors absorption, nevertheless it does not completely explain all the observed phenomena. Simple diffusion alone does not satisfactorily explain the removal of glucose from the intestine when the concentration of glucose is greater in the blood stream than it may be in the bowel. The glucose of the interstitial tissues may be 100 mg while that of the intestines approaches zero yet glucose flows from the intestines to the interstitial tissues.

As to the amount of water which remains in the bowel to maintain water balance, it is the opinion of the writer, that it is the bile which is present in the gut which is of prime importance in determining the amount of residual water which will be retained in the colon. However we shall discuss this more fully later, since this is the principle theme of the paper.

WATER CONTENT OF BLOOD AND TISSUES

Before plunging into the principles of water balance of the colon, let us review briefly some of the well established principles of water control of the body.

Seventy percent of the body is water, which is rep-

resented by the intracellular fluid which comprises fifty percent of the body weight, blood plasma which is five percent of the body weight, and interstitial fluid which is fifteen percent of the body weight.

In health the blood is maintained in a remarkably constant volume since the mechanics of the circulation demand a fairly stationary volume.

Within the body all fluids both intracellular and extracellular have the same osmotic pressure when they are in a state of equilibrium, although temporary osmotic gradients are set up during local physiologic activity. The membranes of the body permit the free passage of water, solutes and certain organic compounds of small molecular size principally urea and glucose; whereas structures of large molecular compounds as protein and lipids are not free to cross membranes by the simple process of diffusion.

Certain chemicals within the body are responsible for the maintenance of osmotic pressure. These are the electrolytes as: sodium, potassium, calcium, magnesium chlorides, bicarbonates, sulphates, etc., (2) carbohydrates as glucose, glycogen, (3) protein substances as urea, amino acids, globulin, albumin, creatine, creatinine, etc., while lipid exert a negligible osmotic pressure because of their slight solubility in water.

The assimilation of practically all substances into the body requires that they arrive at their portal of entry in a solution whose osmotic pressure approximates that of blood plasma. While it is true that the blood stream engages in a free exchange of water with all tissues of the body, its volume nevertheless remains practically constant. There must be then a reservoir upon which the blood volume draws freely and returns water to in order to maintain its rigid volume requirements. This reservoir exists in the extracellular extravascular water which occurs in the interstitial fluid which comprises fifteen percent of the body weight.

Any marked exchange of water either between the body and its environment or between the several tissues becomes primarily a process of drawing upon and replacing the interstitial fluid and is mediated by the blood stream. Extensive changes in the volume of the extracellular extravascular fluid does not seem to disturb its physiologic processes. It is from this reserve that the digestive tract ultimately obtains its 8500 cc fluid which is poured into the gut daily.

In the process of dehydration, it is the interstitial fluid which gives up its water first, while the blood stream and the intracellular fluid retain their volume at the expense of the interstitial fluid.

The fluids of the gut are composed of water which is derived both from ingested fluid and secretions provided by the blood stream and various digestive fluids and electrolytes also provided by these sources. Most of the water and electrolytes in the gut will be reabsorbed later into the blood stream.

Some interesting observations have been made on the fluids removed from the gut. As early as 1852 Bidder and Schmidt (7) demonstrated that large

amounts of fluid were poured into the gut by the blood stream and later resorbed; likewise these solutions resembled the blood plasma chemically. Peters (8) states that in spite of the diversity of the chemical patterns, the secretions of the gastrointestinal tract from the mouth to the rectum including the bile and pancreatic juice have the same osmotic pressure, i.e., the same osmolar concentration as the fluids within the body proper. All of the gastrointestinal secretions including the bile and pancreatic juice are in osmotic equilibrium with the body fluids; furthermore all substances introduced into the digestive apparatus become isotonic with the blood stream before absorption can take place. Irrespective of the nature of the ingested material whether it be plain water, inorganic or organic compounds, it acquires osmotic equilibrium with the blood stream by the addition of water or solutes derived from the blood. This seems to be an essential prerequisite to assimilation.

When osmotic equilibrium is established, then the conditions for absorption are established and assimilation proceeds. While osmotic equilibrium seems to be necessary for absorption, nevertheless it does not fully explain all the known reactions which take place. Simple diffusion is not the entire answer to assimilation from the gut. Thus simple diffusion does not explain the manner by which sugar passes from a low concentration in the intestines to a high concentration in the blood stream.

It is evident that our knowledge of the physiology of the gut is far from complete.

When concentrated glucose enters the gut, fluid is poured into it to bring its osmotic pressure approximately to that of the blood plasma. When this is accomplished then glucose flows into the blood through the activity of an osmotic gradient. However later when most of the glucose has been removed from the intestine and the concentration in the intestine has become lower than that in the blood, nevertheless the intestinal glucose continues to flow into the blood stream although opposed by the osmotic gradient. This phenomenon cannot be explained by any simple known chemical device. It is evident that osmosis, diffusion and osmotic gradients alone do not explain the phenomena of assimilation. There are other forces whose nature remains to be analyzed.

PATHOLOGIC STATES WHICH AFFECT THE WATER CONTROL OF THE BOWEL

There are numerous pathologic states which upset the normal physiologic process of the digestive tract effecting its water balance. Some of these are mild in character, others are severe, or even violent even to the extent of placing the life of the person in jeopardy.

Some of these disturbing processes are interrelated with the salt metabolism as well as the acid base balance in addition to the water balance of the body. It is to Gamble (9, 10) that we are indebted for much of the knowledge of the behavior of water and salt metabolisms of the gastrointestinal tract.

Any clinical condition which gives rise to vomiting causes a loss of water and salts from the gut thereby reducing these reserves in the body. In addition to the actual loss, vomiting also interferes with the normal process of digestion, assimilation and nutrition of the body. Vomiting also interferes with the assimilation of carbohydrate and so tends to cause starvation ketosis. Vomiting removes from the body quantities of water and chlorides, thereby removing the salt reserve of the tissues. If large quantities of salt are lost in this manner, the salt of the tissues will be replaced by bicarbonates thereby producing alkalosis.

In the case of pyloric or intestinal obstruction with pronounced vomiting, there occurs a loss of gastrointestinal contents with depletion of water and chlorides, while at the same time sodium is lost in the urine. If the loss of water and salt is large enough the renal circulatory functions become impaired, the nonprotein nitrogen of the blood will increase and if the process remains unchecked, it will be followed by anuria, shock and death.

Further the obstruction interferes with the processes of digestion, secretion and assimilation of nutrient. Circulation of the gut soon becomes impaired further interfering with the physiologic functions of the bowel retarding the processes of secretion and absorption. Another severe problem which arises with any marked interference of the intestinal circulation is that the bowel loses its ability to remove the soluble gases. These gases which thus remain in the bowel cause further distention aggravating the existing evil thus producing a vicious cycle which if permitted to continue will result in death.

Besides these rather violent clinical syndromes there are numerous milder disorders, of which diarrhea is one. Diarrhea tends to remove water and salts from the body in addition to upsetting the acid-base ratio. Since the stool is alkaline, diarrhea tends to remove the alkaline electrolytes from the tissues producing an acidosis.

Diarrhea occurs in inflammatory states such as typhoid fever where there occurs an inflammation of the bowel, also in toxic states as food poisoning where there occurs either an inflammatory gastroenteritis or a toxic gastroenteritis or both. Further there are numerous other forms of gastroenteritis in which marked diarrhea occurs whose clinical syndrome is still an unsettled matter. Elsewhere (11) we have described epidemics of acute gastroenteritis which tend to occur in the fall of the year in Colorado with almost clock like regularity which we consider to be a form of virus infection. These are characterized largely by diarrhea.

BILE. ITS INFLUENCE ON THE WATER BALANCE OF THE COLON

It is the belief of the writer that bile plays an important role in the mechanism of the water balance of the colon. The writer is unable to find mention of this elsewhere in the literature other than his own

observations. The writer's observations and conclusions are purely clinical in character and are based on the clinical observations of hundreds of patients at the University of Colorado. It is hoped that this report will stimulate laboratory experimentation elsewhere to check these clinical observations.

The colon normally receives the end products of digestion from the small bowel. Its function is to complete digestion, remove the absorbable water which is returned to the general circulation. The colon thus receives the semifluid chyme, reduces its bulk by removing some of the water so that the residual material has a putty like consistency. Should excessive water be removed then a dry constipated stool remains, if insufficient water is removed then diarrhea results. It is obvious that there is an optimum amount of water which remains to form a normal stool which favors normal evacuation.

Sometimes the colon removes an excessive amount of water forming dry fragmented stools. These stools have been known clinically for centuries. Our medical grandfathers referred to them as "greedy colons".

Obviously there must be some substance which controls the amount of residual water in the stool. It is the opinion of the writer that it is the bile which is present in the stool which is of prime importance in determining the amount of water to be retained.

Let us consider some established facts about the behavior of bile in the colon. Bile is both a secretion and an excretion. The amount of bile secreted daily has been variously estimated from about 500 cc to about 1000 cc per day. Most calculations have been based on the fistula method, which Sobotka (12) states cannot give accurate results. Actually we do not know how much bile is secreted daily under basic conditions, because thus far no method has been devised which measures the bile flow under normal conditions. Nevertheless the above estimates give up a basis for discussion. In our work we have taken the figure of 750 cc bile as the convenient estimate of the daily secretion which we regard as a general average of the several calculations reported by the various methods.

Bile serves largely in the function of digestion. During this process it undergoes various forms of chemical disintegration. Incidental to the process of assimilation most of the bile is resorbed into the tissues whence it is returned to the liver for resynthesis into whole bile. In this manner it maintains the balance of the biliary cycle.

The bile that remains in the colon is sacrificed in the process of ejection of waste material, and must be replaced by new bile. Of the bile which is poured into the gut as much as 85 to 90 percent is resorbed into the tissues. The remaining 10 to 15 percent remains to carry on certain necessary and essential functions in the colon even though it is lost to the body in the performance of its duty.

The amount of bile lost in the waste material is in equilibrium with the amount synthesized daily in the liver. Should the daily synthesis of liver bile be reduced then the daily loss will likewise be reduced in

order to maintain the biliary balance of the body.

The sacrificed bile has at least two important functions. One is the long recognized bacterial inhibitory property with its ability to control putrefactive processes in the colon.

The second is its influence on the water balance of the colon. The osmotic pressure of bile is equal to that of blood according to both Sobotka (12) and Peters (2). Sobotka further states that this could have been predicted from its electrolyte content. It is evident that bile possesses the inherent ability to retain water by its presence in the colon.

One of the important functions of the bile therefore becomes the retention of water in the colon and the maintenance of a proper consistency of the feces of optimum water content which favors its ejection from the body even though this bile is lost to the body in the performance of this function.

CLINICAL EVIDENCE. BILIARY CONSTIPATION

Elsewhere we (13) have discussed the clinical evidence in support of this view. We have pointed out that those patients suffering from a negative water balance in the colon have hard dry fragmented stools, that this condition can be successfully corrected by the administration of bile orally either in the desiccated form or as bile salts. We have treated hundreds of patients with biliary constipation successfully by the administration of bile orally.

By biliary constipation we refer to that group of patients apparently suffering from a shortage of secreted bile in the bowel. Obviously we do not include all cases of constipation in this discussion since there are numerous other causes for constipation which we (14) have discussed at length elsewhere. Some of these other causes are faulty diet, insufficient exercise, rectal disease, cardiorenal disease, acute infections, etc., etc.

Biliary constipation is a condition which occurs in middle aged persons of sedentary habits with biliary or hepatic disease which may be organic or functional. It occurs in both sexes but is of greater frequency in women. The age incidence is usually the fifth, sixth and seventh decades of life. It is apt to follow cholelithiasis, acute or chronic cholecystitis, gall bladder dyspepsia, biliaryness or other disorders of the biliary system.

It is primarily characterized by dry hard fragmented stools of reduced caliber or the sheep dung variety. The symptoms are a mixture of gall bladder dyspepsia and spastic colon syndromes. Thus these patients will manifest the "fair, fat, forty and belching gas" syndrome of disturbed gall bladders combined with other symptoms commonly encountered in irritable colon as coated tongue, offensive breath, distress in the epigastrium and both hypochondria, fullness after meals, vague abdominal pains, flatulence, mental and physical sluggishness, abdominal consciousness, intolerance for certain foods as cabbage, cauliflower, radishes, onions, raw apples, canteloupe, peppers, etc.

In the discussion on the physiology of the liver we assumed that 750 cc of bile is secreted daily to maintain normal biliary activity in the digestive tract. We must bear in mind that this is only a convenient estimate based on diverse and separate experiments. Unfortunately we have no way of actually measuring the daily secreted bile under normal conditions. Certainly we have no useful convenient clinical method for measuring the daily flow of bile. Such a method is urgently needed in both clinical and experimental studies. We would like to know how much bile a particular patient secretes daily in order to evaluate more accurately the shortcomings of the biliary system within his body. Under present conditions we are compelled to estimate it clinically. And the best we can do is to state that the biliary flow is either adequate, excessive or insufficient. In biliary constipation we believe that it is insufficient.

The treatment of biliary constipation is both simple and specific. "Since the whole conception of biliary constipation is based on the principle of reduced bile flow, the basis of the treatment is to increase the flow of bile and the only satisfactory manner of doing this is to give either whole bile or bile salts. It accomplishes nothing to give bland diets, vitamins, sedatives, antispasmodics and other therapeutic procedures if the bile salts are omitted". (13) Bile and bile alone is effective in the treatment of biliary constipation. Supplementary treatment may be employed such as selected diets, vitamins, removal of irritating foods and drinks from the diet, sedatives, antispasmodics, rest, relaxation, etc. However it is specifically reiterated even at the risk of becoming repetitious that these procedures accomplish nothing if the bile therapy is omitted.

We have employed Bilron (Lilly) a form of iron bile salts, Kapsseals Desicol (Parke Davis) which is dried soluble whole bile and Ketochol (Searle) a form of oxidized bile acids.

When this is done the results are prompt and efficient. The stools return to normal size, caliber and moisture, likewise most of the distressing symptoms subside. We have treated hundreds of patients successfully by this method.

Although the clinical results bear out the contention that the administration of bile restores the normal water balance to the colon and normal water content to the stool, the manner of action within the digestive tract remains a disputed and debated subject.

Until a relatively short time ago, it was almost universally assumed that bile was the most efficient cholagogue and choleric known. (A cholagogue increases the flow of bile, a choleric increases the secretion of bile) Standard textbooks on pharmacology by Cushny, (15) Sollman, (16) McGuigan, (17) Dixon, (18) Goodman and Gillman (19) as well as the monograph of bile by Horrall, (20), all supported this view.

Recently McGuigan in an excellent discussion on the behavior of bile in constipation challenges his own statement as well as those of his pharmacological colleagues. "In spite of all these statements bile is not

a choleretic," he declares, "it does not stimulate the flow of bile". He states that bile given by mouth does not stimulate the flow of bile rather it simply acts as replacement therapy.

In the field of endocrinology the sharp difference between stimulating and replacement therapy is well established.

According to McGuigan bile taken by mouth does not stimulate the flow of bile, it merely provides material which is easily dissolved in the gut to assume some of the functions of the deficient bile. There is no evidence that it forms new bile or that it stimulates the liver in any way. The apparent increase in the flow of bile after oral administration is merely the ingested bile dissolved, possibly chemically altered and immediately participating in digestive function, much the same as hydrochloric acid would act whether formed in the gastric mucosa or in a test tube.

According to Suhotka (12) bile contains roughly one and one quarter percent solids. Hence this amount of dried inspissated bile is equivalent to 100 cc of bile to which it is easily converted under favorable conditions. In the case of Birlou, McGuigan has estimated that the ingestion of five grains of this preparation will liberate 200 cc of bile.

Although McGuigan insists that ingested bile serves in a replacement rather than a stimulating capacity, nevertheless he admits that it has a useful function in therapeutics where there is an inadequate secretion of bile. "In constipation," he states, "there is a decrease in the flow of bile . . . anything which relieves constipation must influence the flow of bile."

This view supports our conception of biliary constipation and its attendant evils as being due to a reduction in the flow of bile and is relieved by the administration of bile orally.

Our explanation of the helpful action of bile in those patients suffering from reduced bile flow such as occurs in biliary constipation is that it exerts an osmotic pressure on the water of the colon retaining it to maintain an adequate water balance for the colon.

Bile, then, we believe serves the purpose of maintaining water balance within the colon. Its curtailment results in disturbed water balance and dry stools. Its restoration by oral administration restores the mechanism for normal water balance within the colon.

SUMMARY

1. The control of water balance of the bowel is an extremely important clinical problem.

2. The problems of constipation and diarrhea are essentially problems of disturbed water balance of the colon.

3. Existing information on the nature of water balance of the colon is inadequate to explain its behavior.

4. Water is absorbed from the bowel into the blood stream as a solution whose osmotic pressure is ap-

proximately equal to that of the blood serum.

5. The digestive tract secretes daily about 8500 cc of fluid into the alimentary canal most of which is quickly resorbed.

6. Before assimilation of intestinal contents can take place its osmotic pressure must be brought to that of the blood stream by the addition of fluid or solutes from the blood stream.

7. Simple diffusion alone does not fully explain the intestinal absorption of glucose when it flows from a low concentration to a high concentration into the blood stream.

8. All fluids of the body both intracellular and extracellular have the same osmotic pressure when they are in a state of equilibrium.

9. Temporary osmotic gradients are set up during local physiologic activities.

10. All secretions of the digestive apparatus from the mouth to the rectum have the same osmotic pressure.

11. There are numerous pathologic states which alter the normal metabolic processes of the bowel.

12. There exists an optimum amount of water which favors normal stool formation and evacuation.

13. Insufficient removal of fluid from the colon results in diarrhea.

14. Excessive removal of fluid from the colon results in dry hard stools and constipation. It is the "greedy colon" of our medical grandfathers.

15. It is the function of the bile in the colon to control the amount of residual water in the feces. Bile possesses the inherent ability to retain water by the force of its osmotic pressure.

16. About 750 cc of bile is secreted daily, of which 85 to 90 percent is resorbed, the remainder of which serves to control bacterial activity and water balance in the colon. It is lost to the body in the performance of its functions.

17. Persons who have an insufficient secretion of daily bile, likewise have an insufficient amount in the colon to maintain adequate water balance. They develop "biliary constipation" and have dry hard stools as well as other annoying symptoms.

18. The treatment of biliary constipation is both simple and specific. It consists in the oral administration of bile, either the whole inspissated or the bile salts. When this is done the results are prompt and satisfactory. We have treated hundreds of patients with biliary constipation by this method successfully.

19. Bile serves the purpose of maintaining the water balance within the colon. Its curtailment due to a shortage in secretion results in disturbed water balance and dry stools. Its restoration by oral administration restores the mechanism for normal water balance within the colon.

REFERENCES

1. Gamble, J. L.: Extracellular fluid, Harvard Medical School, 1942.
2. Peters, J. P.: Body water, Charles P. Thomas, Springfield, Ill., 1935.
3. Magnus-Levy, A.: The physiology of metabolism, in C. von Noorden, Metabolism and practical medicine, W. T. Keener, 1907, vol. 1, 392.
4. Dill, D. B.: Life, heat and altitude. Physiologic effects of

- hot climates and high altitudes, Harvard University Press, 1938.
5. Rountree, L. G.: The water balance of the body, *Physiol. Rev.*, 1922, 2, 116.
 6. Adolph, E. F.: The metabolism and distribution of water in the body and tissues, *Physiol. Rev.*, 1933, 13, 336.
 7. Bidder, F., and Schmidt, C.: *Die Verdauungssäfte und der Stoffwechsel*, G. A. Reyer, Mitau und Leipzig, 1852.
 8. Peters, J. P.: Water balance in health and disease, in *Duncan Diseases of metabolism*, W. B. Saunders, Phila., 1942.
 9. Gamble, J. L., and Ross, S. G.: The factors in dehydration following pyloric obstruction, *J. Clin. Invest.*, 1925, 1, 531.
 10. Gamble, J. L., and Melver, M. A.: Body fluid changes due to continued loss of external secretions of the pancreas, *J. Exper. Med.*, 1928, 48, 852.
 11. Gauss, Harry: Seasonal gastroenteritis in Colorado, *Amer. Jour. Dig. Dis.*, 1944, 11, 40.
 12. Sobotka, Harry: *Physiological chemistry of the bile*, Williams and Wilkins, Baltimore, 1937.
 13. Gauss, Harry: Biliary constipation, *Amer. Jour. Dig. Dis.*, 1943, 10, 141.
 14. Gauss, Harry: So you feel sluggish today. The causes and treatment of constipation, *The Christopher Publishing House*, Boston, 1942.
 15. Cushing, A. R.: *A textbook of pharmacology and therapeutics*, Lea and Febiger, Phila., 1928.
 16. Sollman, T.: *A manual of pharmacology*, W. B. Saunders Co., Phila., 1942.
 17. McGuigan, H. A.: *Applied pharmacology*, C. V. Mosby Company, St. Louis, 1940.
 18. Dixon, W. E.: *Manual of pharmacology*, E. Arnold and Company, London, 1925.
 19. Goodman, L., and Gillman, A.: *The Pharmacological basis of therapeutics*, The Macmillan Co., New York, 1941.
 20. Horrall, O. H.: *Bile. Its toxicity and relation to disease*, Univ. Chicago Press, 1938.
 21. McGuigan, H. A.: The secretion and excretion of bile in relation to constipation, *Amer. Jour. Dig. Dis.*, 1944, 11, 282.

Statistical Study of Surgery of Biliary Tract Disease Over a Period of Five Years Without Supervised Routine Management

(101 CONSECUTIVELY OPERATED CASES)

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PAPER No. I

THIS report embraces 101 cases of biliary tract disease consecutively admitted to and operated upon at Knickerbocker Hospital, New York City, within the five year period preceding 1937. Without any attempt at standardization of pre or post-operative care, these patients were operated upon by twelve staff surgeons.

This analysis was undertaken for whatever facts could be elicited in an attempt to evaluate the correctness of the multifaceted dicta with which the literature is so replete viz; operate early in acute biliary tract disease; Wesson and Montgomery; Graham and Hoefle; Heuer and others; employ surgical and medical conservatism; Mock and Brown and Dolkart; abandon cholecystectomy for cholecystocholedochostomy; Pribham, et al.

Before attempting this survey it was felt that the mortality rate would be slightly excessive and that scrutiny of the figures would be of considerable value in the preparation of a manual of procedures applicable to the care of patients afflicted with biliary tract disease.

ADMISSIONS AND OPERATIONS— BY MONTHS

January	12	July	7
February	4	August	7
March	5	September	8
April	8	October	13
May	5	November	17
June	10	December	6

From the above it is seen that in the fall and winter months of September through January, with the exception of December, the admissions were higher than in any other season. A suggestion of the possible causes of this are: respiratory infections, more sedentary habits of indoor life and finally the eating of greater amounts of heavier foods. The fewer admissions in December is probably due to the elective nature of many cases of gall bladder disease and the yuletide holidays of this month.

SEX

Seventy-two cases of biliary tract disease occurred in females as compared with twenty-nine males, a ratio of 2.6 to 1.

RACE

Ninety-seven of the patients were whites to only four colored. The colored patients were all females. (The dearth of colored females, and the total absence of colored males, provokes the question of the incidence of cholecystitis in this race. In this group, were the colored patients taken to another hospital, or is the incidence of gall bladder disease low in the negro?).

AGE RELATIONS

Average Age of All Patients	42.9 years
Extremes of Age	19 years and 74 years
Average Ages of Males	45.9 years
Average Age of Females	41.1 years
The average age of the females at 41 years is five years younger than in the males, at 46 years.	

DURATION OF HISTORY ON ADMISSION

1 to 5 days	12 cases
1 to 3 weeks	15 cases
1 to 10 months	10 cases
1 to 20 and more years	60 cases

In seventy cases upper abdominal symptoms existed for periods of one month to twenty years or more, while only in twenty-seven cases did symptoms exist from one day to three weeks before admission to the hospital. As will be shown later in this report, those cases in which acute symptoms were present, arose in both of the above groups.

DESCRIPTION OF PAIN

"Sharp"	27	"Gas"	2
"Severe"	17	"Knife-like"	2
"Colicky"	12	"Moderate"	1
"Cramps"	5	"Shooting"	1
"Stabbing"	5	"Pressure"	1
"Pain"	5	"Excruciating"	1
"Indigestion"	3	"Acute"	1
"Cutting"	2	"Distress"	1

There was found no absolute parallelism between the type of pain stated by the patient and the presence of lithiasis in the biliary tract. However, it is interesting to note that in only four instances out of twenty-seven, were stones not found at operation when the pain was described as "sharp." Stones were not found in one case and not stated in another of twelve cases when pain was said to be "colicky." They were present in every one of 17 patients when the pain was "severe."

When pain is said by the patient to be "severe," "colicky" or "sharp" the probability of stones being present in the biliary tract is about 90% if any conclusion is justified by this analysis.

LOCATION OF PAIN

Right Upper Quadrant	56 cases	Right Chest	1 case
Epigastrium	36 cases	Interscapular	1 case
Right Lower Quadrant	8 cases	Right Abdomen	1 case
Umbilical	3 cases	Right Arm	1 case
General Abdominal	2 cases	Right Back	1 case

Stones were absent seven times or 12.5% in 56 patients with pain located in the right upper quadrant and absent twice or 5.5% in 36 patients when pain was located in the epigastrium. When biliary tract disease is present and pain is located in the epigastrium or right upper abdominal quadrant, bladder or duct stones are most probably present by 94.5% and 87.5% respectively.

RADIATION OF PAIN

Region	Total	With	Without
	Cases	Stones	Stones
To Right Scapula	15	8	7
To Back	12	11	1
To Right Shoulder	11	4	7
To Right Back and Shoulder	4	3	1
To Right Lower Quadrant	3	3	0

One Case Each Gave a History of Radiation to.—
(a) Rt. Upper Quadrant (b) Back and Both Shoulders.
(c) Rt. Shoulder and Left Side, (d) Left Breast and

Right Shoulder, (e) Left Shoulder and Left Back (f) Laterally, (g) Right Flank, (h) Right Lower Quadrant and Right Back (i) Right Scapula and Right Shoulder (j) Chest and both Shoulders, (k) Left Scapula, (l) Right Flank.

Pain radiated to the right scapula, back and right shoulder regions 15, 12 and 11 times respectively. Only in these instances is the number of cases large enough to consider statistically. When the locus of radiation was the right scapula, the incidence of stones was 53.3%. Stones were present in 91.7% of cases when the pain radiated directly through to the back while they were present in only 36.5% in cases showing radiation to the right shoulder. Stones, therefore, are more probably present when pain is radiated to the back than to any other location.

Unfortunately, the charts did not contain sufficient detailed history concerning selective food intolerance, provocation or cessation of pain, nausea, vomiting, etc., to be of any value statistically.

JAUNDICE

Clinical Jaundice	22 cases
Conjunctival Icterus only	2 cases
Doubtful Icterus	2 cases

No stones were found at operation in 4 of the 22 cases giving a previous history of icterus. Likewise, one of the two cases of historical conjunctival jaundice, yielded no stones at operation. A solitary stone was found in the choledochus in one of two cases of doubtful cholelithiasis. Out of twenty-four cases giving a positive history and two cases of doubtful history of jaundice, in six cases or 23.8% no concretions could be found in the biliary tract at operation. Therefore, whatever the cause of the jaundice in these cases, no obstruction was present at the time of surgery.

OPERATIONS

Ectomy	89 cases
Ectomy & Appendectomy	4 cases
Ectomy & Herniotomy	1 case
Ectomy & Fistulectomy	1 case
Ostomy	5 cases
Died on Oper. Table	1 case

FATE OF OSTOMIES

- 1 Case died—no stones—chronic myocarditis.
- 1 Case died—many stones—hydrop, acute hepatitis.
- 1 Case died—stones—acute hemorrhagic pancreatitis.

In this series of 101 cases, cholecystectomy was performed 95 times or in 94% and cholecystostomy in five instances or 4.95%.

Three of the five cases or 60% in which the gall bladder was drained died. The causes of death were chronic myocarditis, acute hepatitis and acute hemorrhagic pancreatitis. Two of these cases were with stones and one without.

The selection of these three cases was not ideal. The operation chosen was the most conservative, however, in the face of the condition of the patient preoperatively.

MORTALITY RATE

Cases Operated	total 101
Post-Operative Deaths	14
Deaths on Operating Table	1
Deaths	total 15
Percentage Mortality	14.85%

CAUSES OF DEATH

No.	Diagnosis	Cause of Death
192-31	Chronic Cholecystitis	General Arterio-sclerosis
	Cholelithiasis	Chronic Myocarditis
2577-31	Chronic Cholecystitis	Cerebral Hemorrhage
1432-32	Acute Cholecystitis	Bilateral Broncho-pneumonia
	Cholelithiasis	
879-33	Chronic Cholecystitis	Shock-Acute Hepatitis
	Cholelithiasis	
2286-33	Chronic Cholecystitis	External Biliary Fistula
	Cholelithiasis	
2931-33	Chronic Cholecystitis	External Biliary Fistula
	Cholelithiasis	Abscess of Pancreas
	Abscess of Pancreas	Pylephlebitis
238-34	Acute Suppurative Cholecystitis	Acute Diffuse Peritonitis
	Cholelithiasis	Right Lobar Pneumonia
	Acute Diffuse Peritonitis	
975-34	Acute Suppurative Cholecystitis	Infarct of Spleen
	Cancer of Stomach	Acute Pancreatitis
1444-34	Hydrops of Gall Bladder	General Arteriosclerosis
		Chronic Valvular Disease
		Auricular Fibrillation
1458-34	Acute Suppurative Cholecystitis	Acute Diffuse Peritonitis
	Cholelithiasis	
	Perforated Gall Bladder	
	Cholecysto-duodenal fistula	
	Acute Diffuse Peritonitis	
2212-34	Chronic Cholecystitis	Acute Hemorrhagic Pancreatitis
	Cholelithiasis	
	Acute Hemorrhagic Pancreatitis	
3085-34	Chronic Cholecystitis	Peritonitis
	Perforated Duodenal Ulcer	
3378-35	Acute Suppurative Cholecystitis	Streptococcus Viridans, Septicemia, Secondary Hemorrhage
	Cholelithiasis	
35-85-35	Chronic Cholecystitis	Acute Pancreatitis
	Cholelithiasis	
104-36	Acute Pancreatitis	Acute Diffuse Peritonitis
	Acute Diffuse Peritonitis	Septicemia, Abscess of Liver, Gangrene of Duodenum and Hepatic Flexure, Infarct of Heart

In the fifteen mortalities, acute diffuse peritonitis occurred six times as the cause of death. Chronic circulatory disease was responsible for three. Pneumonia was the cause of death in one case and contributed in a second case. Acute hemorrhagic pancreatitis accounted for three deaths and abscess of the pancreas contributed to a fourth. Acute hepatitis contributed to post-operative shock in one case that died. External biliary fistula was the cause in one and a complication in two mortalities. Pylephlebitis and liver abscess occurred one time each in the mortality series. Lastly, secondary

hemorrhage was the cause of one death in a case of green streptococcus septicemia.

A mortality of 14.85% is definitely high as compared to the usual 10% as shown by most published reports on consecutive biliary tract operations.

Contributing to this 15% mortality are three cases of grave circulatory disease, three cases of acute hemorrhagic pancreatitis and one case of pancreatic abscess. In many of the low mortality series these would not be classified as biliary tract disease deaths, but rather under their respective headings. Under these circumstances our mortality then would be reduced to the comparatively low figure of 8.9%.

Rather than resorting to any statistical manipulations, every case which had any kind of operation upon the biliary tract has been so classified.

Ninety-seven cases were drained with from one to several drains consisting of: cigarette, penrose, tissue and tubes.

Three cases were closed without drains, all lived.

TYPE OF INCISION

Vertical or Longitudinal	59 cases
Transverse or Oblique	40 cases
Vertical and Transverse	1 ease
Died on Table	1 ease
Total	101 cases

There is a sufficient number of both the vertical and oblique types of incision to afford a comparison of the incidence of incisional hernia in each. This will be discussed with the follow-up data.

POST-OPERATIVE WOUND INFECTIONS

Remained Clean	92 cases
Became Infected	8 cases
Total	100 cases

Percentage of Post-Operative Infections 8%

All wounds which became infected after operation were in patients having stones and some had pus in addition.

These cases are considered borderline or potentially infected cases rather than clean cases becoming infected.

PERIOD OF HOSPITALIZATION

Average Stay from Admission to Discharge	
or Death	25.9 days
Average Stay from Admission to Operation	6.74 days

These figures will be broken down and further analyzed later in the paper. Suffice it to say that a period of hospitalization of twenty-six days is from seven to nine days longer than is found in some hospitals. Our figure is considerably increased too, on account of one case which was operated upon on the eighty-sixth day of hospitalization.

DIAGNOSIS

Chronic Cholecystitis	23 cases
Chronic Cholecystitis with Stones	53 cases

Acute Cholecystitis	5 cases
Acute Cholecystitis with Stones	20 cases
Total Number of Cases with Stones	73 cases
Cases with Stones only in Gall Bladder	57 cases
Cases with Stones only in Choledochus	11 cases
Cases with Stones in both Gall Bladder and Choledochus	5 cases

Percentage of Total Cases Having Stones 72.3%

The above diagnoses were those made post-operatively by the twelve operating staff surgeons.

In this series of 101 consecutive cases of cholecystitis, there were 76 chronic and 25 acute cases. Of the 76 chronic cases there were stones in 53 or 70%, while in the 25 acute cases 20 or 80% had stones.

Stones were present somewhere in the biliary system in 73 instances or 72.3%. Concretions were found in the gall bladder, 57 times or in 56.4% of the series; 11 times or in 11% in the choledochus and 5 times or in 5% in both the gall bladder and choledochus simultaneously.

A fact worthy of mention is the higher incidence of stones in acute cholecystitis, 80%, than in chronic biliary disease, 70%. These figures are in agreement with those from most other sources.

ANALYSIS OF ACUTE CASES

Because of the conflicting evidence concerning the propitious time to operate in cases of acute cholecystitis, the analysis of these cases will be carried into their minutiae.

Total Acute Cholecystitis	25 cases
Percentage Acute Cases in Series	24.75%
Number of Acute Cases Perforated	4 cases
Percentage of Perforated Cases	16%
Number of Acute Cases Gangrenous	2 cases
Percentage of Acute Gangrenous Cases	8%
Number of Acute Cases with Stones	20 cases
Percentage of Acute Cases with Stones	80%
Mortality of Acute Cases	6 cases
Percentage Mortality in Acute Cases	24%

In this series of 101 cases, twenty-five or 24.75% were acute. The gall-bladder was perforated in four or 16% of the acute series. In two instances or 8% of the acute cases there was gangrene of the gall bladder. Twenty of the twenty-five cases or 80% had stones. Six of the acute cases died, a mortality of 24%.

We now have for consideration six cases of acute cholecystitis that died and nineteen cases that recovered.

The preoperative hospital stay for the six fatal cases averaged 28.2 days. However, in one instance the patient remained in the hospital 86 days before operation. Excluding this one case, the average for the remaining five cases is 16.6 days. The actual preoperative days in the hospital for these six fatal cases was: 6, 6, 9, 18, 44 and 86 days.

In the nineteen acute cases that recovered, the average preoperative hospitalization is 4.9 days, as compared to the minimum of 16.6 days for those that died.

Upon survey of the figures it is found that 13 acute

cases were operated upon between the day of admission and the 6th hospital day, without a fatality. In other words:

Total Acute Cases Operated During first 5 days in hospital 13 cases

Number of Acute Cases Operated during first five days in Hospital with Recovery 13 cases
Percentage of Recoveries 100%

5 cases were operated on the day of admission.

4 cases were operated first day after admission.

1 case was operated second day after admission.

2 cases were operated four days after admission.

1 case was operated five days after admission.

The mortalities therefore all occurred in those cases operated upon during and beyond the sixth hospital day.

It is perhaps of interest to note in passing that in the four perforated cases, only one case lived. This patient was operated upon on the day of admission. The remaining three cases were operated upon on the 6th, 18th, and 86th days respectively. Both cases with necrosis of the gall bladder lived, having been operated on the 7th and 18th day of hospitalization.

In the above thirteen acute, recovered cases the total hospitalization averaged 27.1 days in comparison with 28.1 days average for the entire group of 25 cases of acute cholecystitis.

Before drawing any conclusions from the above data concerning the proper time to operate in acute biliary tract disease, it would be well to examine the duration of the biliary symptoms in this series of twenty-five acute cases.

DURATION OF BILIARY SYMPTOMS IN (6) DEATH CASES

From 5 to 10 days	3 cases
Two Weeks	1 case
Ten Years	1 case
Several (?) Years	1 case

DURATION OF BILIARY SYMPTOMS IN (19) RECOVERED CASES

3 to 5 days	3 cases
6 to 19 months	4 cases
1 to 20 Years	9 cases
Several Years	1 case
"Chronic"	1 case
Not Given	1 case

Both cases of cystic gangrene recovered. Definite biliary symptoms were present one year and eight years. They were operated on the seventh and 18th days respectively, after admission.

In the four perforated cases, symptoms were present; four days, five days, two weeks and ten years, prior to admission to the hospital. The only recovered case was that in which the initial attack started four days prior to admission and the patient was operated on the day of admission. The remaining three perforated cases were not considered favorable operative risks until the 6th, 18th and 86th post-admission day, if at all.

It is to be noted from the above data that while definitely the most expeditious time to operate for acute biliary tract disease is within 48 hours of the onset of the attack, in many of our patients it is impossible to ascertain the time of transition of the chronic state into the acute process. Secondly, in most instances, the condition has advanced to the stage where supportive measures rather than surgery are indicated.

STONES IN (6) ACUTE CASES THAT DIED:

Stones Present	4 cases
No Stones Present	1 case
Not Stated	1 case

STONES IN (19) ACUTE CASES THAT RECOVERED.

Stones Present	15 cases
No Stones Present	4 cases

The presence of stones in this and most other series is about 80%. Stones are about equally distributed in those cases that died and in those that recovered.

SEX IN ACUTE CASES

Females	15
Males	10

The relation of females to males in the entire series of 101 cases of biliary tract disease, acute and chronic, was 2.6 females to 1 male. In acute biliary tract disease the relationship changes to 1.5 female to 1 male. Mortality, however, was equally distributed between the sexes in the six acute cases that died.

AGE DISTRIBUTION

Average Age in all 25 acute cases.....	48.2 years
Average Age in 19 surviving cases.....	46. years
Average Age in 6 fatal cases.....	55. years

The age of the 101 patients with biliary tract disease averaged 42.9 years. Those 25 patients with the acute form, however, averaged 48.2 years. In this latter group the 19 surviving victims averaged 46 years, while the six patients who died averaged 55 years of age. The average age of the fatal patients was nine years greater than that of those who survived. Disregarding all other causes of death, an increase of ten years over middle age is an important factor in the mortality rate of any major surgical procedure.

FOLLOW-UP STATISTICS

Eighty-six post-operative patients were discharged from the hospital. Of this group 44 patients or 51.2% were followed.

The length of the follow-up period ranged from one to 80 months, an average of 25.1 months.

Eight of the forty-four followed patients were suffering definite pain, a percentage of 18.18%.

Ten of the forty-four gave a definite history of intolerance to fatty foods, a percentage of 22.7%.

No case had jaundice post-operatively—none had alchoolic stools.

36 or 82% of the 44 patients considered themselves cured.

7 patients or 15.8% considered themselves improved.

1 patient or 2.3% of the group was considered unimproved.

6 or 13.6% had persistent tenderness in the Mayo-Robson area in the sitting posture.

In 13 operations the oblique or transverse incision was made. The upper right rectus incision was used in thirty-one cases.

Incisional hernia did not occur in any of these thirteen transverse incisional cases. Incisional hernia did occur in five cases or 16.1% in the 31 cases in which vertical incision was made.

Before summarizing these results, it is interesting for the sake of comparison to cite statistics from other sources.

Wesson and Montgomery of the Mayo Clinic in reporting upon 76 operated cases of acute cholecystitis, show 3 deaths, a mortality of 3.9%. The gall bladders in 2 or 2.6% had ruptured and in another or 1.3% it was gangrenous.

In 16 instances of the 76 cases or 21% the gall bladder had ruptured. In another 18 cases or 24% gangrene was present. Therefore in 45% rupture was present or imminent.

Cholecystectomy was performed 61 times or in 80%. Due to the condition of the gall bladder, cholecystostomy was the operation of choice and expediency in 15 cases or 20%. There were no deaths in the 15 ostomies.

13 cases were definitely acute upon admission and were operated upon within 12 hours. The duration of symptoms averaged 4 days before operation. The post-operative hospital stay was 15 days.

In 41 cases the duration of symptoms prior to admission averaged 7.6 days. They were operated upon 5.6 days later and remained post-operatively 19.2 days.

In 22 cases the elapsed time between the last attack and operation was one week to 3 months. They were discharged 19.1 days after operation.

Perforation was present in only one of the 14 cases subject to immediate operation in contradistinction to 12 perforations out of the 41 cases in which operation was delayed. According to these findings early operation abbreviated the time necessary for gangrene and perforation to supervene.

Graham and Hoefle of Brooklyn Methodist Hospital cite a series of 167 cases of acute biliary tract disease operated upon within 48 hours of the incidence of symptoms. Six cases died, a mortality of 3.59%. These fatalities do not include such conditions as acute hemorrhagic or suppurative pancreatitis, only acute cholecystitis.

Graham and Hoefle, furthermore, state that in a series of 100 consecutive cholecystectomies at the same hospital the mortality rate was 9%. However, in 51 cases which were operated upon within 48 hours, two died, a mortality of 3.92%. The mortality was 22.7% when operation was delayed more than 5 days.

Again the figures definitely indicate necessity of early operation.

Pennoyer of Roosevelt Hospital gives a mortality of 10% in a series of 100 cases of acute biliary tract disease. The policy there was to delay operation as long as possible. The proper inference here in the light of

preceding figures would be; earlier operation would have reduced the mortality.

While achieving mortality rates is our ultimate aim, clinical and scientific honesty must still be retained. For example; if a case primarily of acute purulent cholecystitis with associated acute purulent pancreatitis recovers from cholecystectomy or ostomy it is classed as a cured case of acute cholecystitis. On the other hand had the case succumbed to operation it should not be discarded from consideration as acute cholecystitis because the diagnosis then became acute purulent pancreatitis and because of the high mortality in this condition the fatality therefore belongs in that category.

Likewise, death precipitated by cholecystectomy or any other surgical procedure in an old hypertensive arteriosclerotic patient is still a death, the untimeliness of which should be charged to the surgeon's bad judgment in selecting this patient for surgery. Statistical deletion of such fatalities thwarts our ambitions.

Every fatality should be included in these statistical studies. Every fatality should act as a challenge to our judgment in the proper selection of cases and skill in the surgical management pre and post-operatively of subsequent cases, rather than sharpening our cunning to obtain better competitive figures for publication than other institutions, by improper deletion of unfavorable results.

Graham shows a mortality of 22.7% in 51 cases, a series of 100 consecutive cholecystectomies in which operation was delayed more than five days.

Pennoyer, gives a mortality of 10% in a series of 100 cases of acute cholecystitis in which the tendency was to delay operation.

While Wesson and Montgomery show only three deaths out of a series of 76 operated cases of acute cholecystitis a mortality of 3.9%. In only 13 cases was operation performed within five days. However, in 15 cases or 20% ostomy was performed without a single fatality. In each instance gangrene or perforation was present. Furthermore, 45% of this entire series had either perforation or gangrene. In the 76 cases no fatality occurred in any of the 15 on whom cholecystostomy was performed. Three of the remaining 61 cases of cholecystectomy died, a mortality of 5%.

The chief facts to be deduced from a comparison of these figures is the choice of operation to fit the particular case, rather than the universal application of cholecystectomy.

In our series with a mortality of 15%, Graham's of 22.7% when operation was delayed more than 5 days and Pennoyer's 10% mortality, strongly suggests to me laxity in the proper choice of cases for operation, and secondly, inadequate consideration of the type of operation to apply.

In our hospital, and I assume in most hospitals, it is impossible to operate upon patients as early as 48 hours after the onset of symptoms, because many days or weeks usually elapse before admission. Also in almost one-third of the instances it is humanly impossible to differentiate between the acute, and chronic types (30% in the Mayo series).

Considering the results in our own 101 cases of chronic and acute cholecystitis, combined, and those in acute cholecystitis from representative sources, the following conclusions seem justified.

CONCLUSIONS

(1) The highest incidence of admissions for cholecystitis is in the fall and early winter months, although it is not a seasonal malady.

(2) Two and one-half times as many females as males are afflicted.

(3) The colored race seems less susceptible than any other in our hospital district.

(4) The disease crystallizes early in the 4th decade in the female and in the middle of the same decade in the male.

(5) 5.60% of our cases have histories of cholecystitis for from one to twenty years and more before applying for relief. Twenty-five percent have suffered attacks for from one week to one year, while the remainder give a history of only one to five days.

(6) In about 90% of patients describing their pain as being "Severe"—"Colicky" or "Sharp" stones were present in some part of the biliary tract.

(7) Biliary tract concretions were present in 94.5%, when pain was located in the epigastrum and present in 87.5% of patients with cholecystitis when located in the right upper quadrant.

(8) Stones were present in 91.7% of cases when pain was radiated directly posteriorly to the back.

(9) Jaundice was found in only about one-fourth of the cases. In about one-fourth of the previously jaundiced cases no stones were found at operation.

(10) Ectomy was performed 95 times to 5 ostomies, a ratio of 19 to 1.

(11) Our mortality of 15% could most probably have been lowered by medical management rather than formidable surgery in some of those patients with chronic degenerative circulatory disease and in those stoneless cholecystides. And in still others, death could have been averted by employing drainage rather than removal of the gall bladder.

(12) No herniae followed the transverse type of incision. In the longitudinal right rectus incision hernia resulted in 11.3% of the cases followed.

(13) Post-operative wound infection occurred in 8%. All of these cases were drained. All had stones, some had pus in addition. No infections were severe. All such cases must be considered "borderline" cases that became infected.

(14) The average total hospitalization was 25.9 days. The average pre-operative hospitalization was 6.7 days.

(15) The diagnoses were all surgical and made finally at the time of operation.

(16) In the 25 acute cases; 16% were perforated and 8% were gangrenous at operation. Six of the cases or 24% died. The six fatal cases remained in the hospital 28.2 days before operation.

The 19 acute cases that survived averaged 4.9 days in the hospital pre-operatively. All acute cases, 13 in number, operated upon before the 6th hospital day

survived. The total hospital stay for all acute cases was about 28 days.

(17) The incidence of stones at 80% in the acute cases was 10% higher than for the entire series.

(18) The average age for biliary tract disease in the entire series was 43 years. The average age in the acute cases was 48.2 years. The average in the cases that survived operation was 46 years and the average age in the

fatal cases was 55 years.

(19) 51.2% of the operated patients were followed in the Out-Patient Department for an average of 25.1 months with the following results:

- (a) 82% of the patients considered themselves cured.
- (b) 15% considered themselves improved.
- (c) 2.3% were unimproved.

Statistical Study of Surgery of Biliary Tract Disease Over a Period of Five Years Under Supervised Routine Management

(106 Consecutively Operated Cases)

By

PRO V. PREWITT, M.D.
NEW YORK, N. Y.

PAPER No. II

THE past few years have witnessed almost epochal strides in the development of new and safer anesthetics and methods of application.

During this same interval astounding reductions have occurred in the morbidity and mortality in many surgical conditions from the parenteral introduction of fluids and electrolytes.

Simultaneously with these investigations and reports, are the enlightening studies on the pathological physiology of the liver with its subsequent influence upon surgery in general and upon surgery of the biliary tract in particular.

During the past several years the literature abounds with researches upon the etiology, pathology and clinical manifestations in biliary tract disease. Some of the reports embrace such colossal numbers as 5000 cases, over a period of twenty years. Others comprehend a mixture of private and clinic patients and still others include only private patients.

Shortly more than five years ago it was decided at Knickerbocker Hospital, New York City, to incorporate all of the newer and pertinent tests and methods which gave promise of merit into a manual for the routine management of all cases of biliary tract disease.

In the evolution of this routine, any adamant rules of standardization have been avoided.

This paper, therefore, is a report upon the application of this routine, firstly as regards the pre-operative diagnostic and preparatory procedures; secondly, the suggested operative details, thirdly, the post-operative care of the patient; and fourthly, the analysis of findings and results.

The 106 consecutive cases of biliary tract disease, all of which were clinic patients, were operated upon by 11 staff surgeons in the five year period between April 1937 and June 1942. The majority were acutely ill enough to be admitted by ambulance, the remainder being sent in by the Out-Patient Gall Bladder Service.

These patients comprise the many nationalities residing in the upper west side of Manhattan.

I PREOPERATIVE ROUTINE

Upon admission of the patient a careful history was taken, physical examination and routine laboratory procedures necessary for immediate diagnosis were executed. Simultaneously, sedation, glucose and electrolyte infusions and other necessary preoperative measures were expedited in case immediate surgery was indicated.

If after consultation with the attending surgeon, operation was deferred, the case was classified clinically as one of the following, pending continuous observation and further investigation.

The clinical classifications were:

- (a) Acute Cholecystitis without Jaundice.
- (b) Acute Cholecystitis with Jaundice.
- (c) Chronic Cholecystitis without Jaundice.
- (d) Chronic Cholecystitis with Jaundice.
- (e) Biliary tract Obstruction in the absence of a Gall Bladder.
- (f) Silent Jaundice.
- (g) Acute Pancreatitis.
- (h) Biliary Dyskinesia or Dyssynergia.

Each of these classifications is tantamount to a provisional diagnosis which is subject to change following adequate study.

For each of the preceding diagnoses there is a corresponding list of routine diagnostic procedures, similar to the one presented below. These procedures were executed provided surgery was deferred sufficiently long.

DIAGNOSTIC PROCEDURES

- Clinically Chronic Cholecystitis with Jaundice.
- 1. Complete Blood Count.
- 2. Sedimentation Rate.
- 3. Blood Non-Protein Nitrogen.

4. Blood Urea Nitrogen.
5. Blood Cholesterol.
6. Serum Amylase.
7. Blood Prothrombin.
8. Blood Coagulation Time.
9. Bleeding Time.
10. Blood Typing.
11. Icterus Index.
12. Hanger Cephalin Flocculation Test.
13. Alkaline Serum Phosphatase.
14. Urinalysis.
15. Urinary Bilirubin.
16. Galactose Tolerance Test.
17. Hippuric Acid Test for Liver Function.
18. Urobilinogen Test.
19. Duodenal Drainage for Cholesterol Crystals and Calcium Bilirubinate Granules.
20. Flat X-Ray Plate of Abdomen for Stones.

From such a list of diagnostic tests it is evident that many of them are common to all types of biliary tract disease. The purpose of these procedures is firstly an evaluation of the physiological state of the patient and secondly the differential diagnosis.

While further preparation for surgery of all patients was essentially the same, certain differences were necessary, depending upon the presence of jaundice.

In the absence of jaundice a daily diet of 3000 calories was given for four days. This diet consisted of carbohydrate 70%, protein 25% and an absolute minimum of fat, 5%. This was achieved by giving large quantities of gelatin suspended in lemonade.

In addition to the usual pan-vitamin intake, every patient was given sufficient vitamin K to elevate and maintain the prothrombin level to as near 100% as possible.

To insure efficient vitamin K activity, sufficient cholericetics were administered three times daily by mouth.

A minimum daily fluid intake of 2000 c.c. was maintained. Citrated blood transfusions were given preoperatively if the red blood count were below three million cells per cubic centimeter.

Medical consultation was obtained whenever (a) the blood urea or non-protein nitrogen partitions were elevated; (b) when sugar and acetone bodies were present in the urine and (c) if there were any evidence of cardiac or circulatory incompetency.

In all instances where possible, in these less urgent non-jaundiced patients, operation was further delayed (a) when the serum prothrombin was less than 80% (b) when the blood retention of phenoltetraiodophthalein was 50% or over; (c) when the hippuric acid liver function test was less than 1.5 grams hippuric acid in four hours (d) when blood urea and non-protein nitrogen were excessive and (e) if diabetes were present to excess and uncontrollable.

In the preparation of the jaundiced patient for surgery, the purpose of all the above procedures must be achieved, however, the method varied in certain

instances. For example, in the completely obstructed patient, one of the water soluble vitamin K preparations was administered parenterally because of acholia of the intestinal tract.

In the patient unable to retain sufficient carbohydrate and protein, when administered orally, blood transfusions and glucose infusions were substituted.

Realizing the gravity of cholemia as a complication because of the accompanying liver damage, and the contributing tendency to hemorrhage, each jaundiced patient was given a whole blood transfusion of 500 c.c. on the day preceding operation. Also six milligrams of water soluble vitamin K preparation was given intravenously immediately preceding the operation.

As the final step in the preoperative preparation and in anticipation of an emergency during the operation, a slow venoclysis with 10% glucose in saline was started before even the initial phase of the operation. By this procedure intravascular stimulation or replacement of hemorrhage could be effected momentarily.

2. ROUTINE AT OPERATION

It must be emphasized here especially, that the routine was not meant to be a fixed standardization but merely a suggested sequence of procedures designed to obtain most information concerning the disease and be of greatest benefit to the patient and service.

The operating surgeon was urged to record his findings concerning the entire hepato-biliary tract, pancreas, stomach, duodenum, appendix, kidneys, etc., immediately upon the completion of the operation.

It was further urged that cultures and tissue specimens be taken carefully for subsequent microscopic study. Biopsy of the liver was also requested in each case.

The manual contained details of technique for opening and closing the abdomen, the placing of drains, removal or drainage of the gall bladder, exploration and intubation of the common bile duct, the performance of cholecystostomy or enterostomy and finally the several prevailing methods for reconstruction of the common duct in benign stricture, including the vitalium cannula and hepatocholangio-enterostomy.

At the outset, cholangiograms were taken routinely in the operating room in cases suspected of common duct obstruction. This procedure was abandoned because of expense and the necessity for extra personnel. The writer advocates this procedure, since in borderline cases it obviates unnecessary choledochal exploration thereby lowering the rising incidence of common duct stricture arising from this operation.

In order to facilitate the determination of the choice of operation to apply in certain cases of biliary tract disease, a detailed list of indications for the more frequent operations was incorporated in the manual. viz:

INDICATIONS FOR CHOLECYSTOSTOMY

1. Very aged and otherwise poor surgical risk patients.
2. Advanced myocardial insufficiency in whom re-

- ief from pain of calculi was imperative.
3. Advanced renal arterial degenerative disease.
 4. As first stage in certain poor risk cases of empyema of the gall bladder.

INDICATIONS FOR CHOLECYSTECTOMY

1. The presence of calculi.
2. Thickened gall bladder wall, acute or chronic.
3. Gray or pink wall instead of normal slate blue.
4. Adhesions on any part or whole of gall bladder.
5. Encasement of gall bladder by fatty envelope.
6. Presence of Lund's sentinel gland at the junction of the cystic and common ducts.
7. Acute hepatitis associated with acute choleystitis.
8. Chronic subcapsular fibrosis of the right hepatic lobe radiating from the gall bladder.

INDICATIONS FOR CHOLEDODCHOTOMY

1. Preoperative signs or symptoms of common duct obstruction.
2. Transient bile in the urine without jaundice.
3. Small contracted gall bladder with or without stones.
4. Presence of small stones in the gall bladder.
5. Palpable mass or masses in any of the bile ducts.
6. A dilated cystic duct.
7. A dilated common duct.
8. Cholangitis with irregular thickening of the common and hepatic ducts.
9. Fibrosed, contracted common duct.
10. Presence of turbidity or flocculation in the material aspirated from the common duct.
11. Presence of non-neoplastic thickening or induration in the head of the pancreas suggesting ampillary stone with reflux of bile into the pancreatic duct.

ROUTINE POSTOPERATIVE CARE OF THE PATIENT

The following measures common to all cases of biliary tract disease were instituted after operation;

Daily infusions of three liters were given until the oral intake of fluids exceeded the output. If the patient's condition seemed poor on the day of operation, an adequate transfusion was given, if appreciable continuous blood loss, two hundred cubic centimeter blood transfusions were recommended at sufficiently frequent intervals. In cases of biliary asthenia, marked by anorexia, nausea, dehydration and a weak, rapid pulse and low pulse pressure, adequate transfusions of whole blood were administered as indicated.

Twenty milligrams of Thiamine Chloride was administered daily until three grams of brewers yeast was tolerated by mouth.

Fifty milligrams of Cevitaminic Acid were given hypodermically, until tolerated orally.

For perceptible bleeding or blood prothrombin lower than 80%, three milligrams of Vitamin K were given every three hours by mouth or every four hours hypodermically if not tolerated orally.

Oral administration of Vitamin K was continued if jaundice were present, even if the prothrombin level were between 80% and 100%.

Various preparations of the conjugated bile acid were administered parenterally or by mouth. On occasions when bile loss was great from a sinus, this was returned to the patient by gavage tube. By these agencies was assured; sufficient choleresis to flush the bile ducts, efficient action by Vitamin K and increased blood flow and oxygenation of the liver.

To restore and maintain the functional integrity of the liver, postoperatively, the same high carbohydrate, high protein and low fat diet was used as in preparing the patient for surgery.

Intra-abdominal drains, most usually simple penrose tubing, were removed on the fifth postoperative day, an adequate sinus tract having formed in that period.

All silk skin sutures were removed usually on the 6th postoperative day.

In case of choledochostomy with a "T" tube in situ the following added routine measures were executed;

The "T" tube was firmly healed in its sinus tract on the twelfth postoperative day. At this time diodrast, because of its high radiopacity was injected into the biliary tract under fluoroscopic control. By this harmless procedure could be determined; the presence and location of any biliary obstruction and the degree of sphincteric tonus.

Filling of the intra and extra-hepatic duct system without overflow into the duodenum was interpreted to mean that the intraductal pressure was more than 160 millimeters of water and that the sphincteric tonus was great enough to withstand this pressure.

If on the other hand, overflow into the duodenum precluded filling of the biliary tree, sufficient morphine was administered to cause a closure of the sphincter and thus permit filling of the bile ducts.

In the absence of obstruction, the long arm of the "T" tube was clamped continuously unless epigastric pain or distress gave evidence of back pressure within the duct system, due to spasticity of the sphincter. If pain were experienced, the tube was opened for fifteen minutes at intervals of two hours until it could be clamped continuously for two days without symptoms.

At this time the actual resistance of the sphincter was measured directly with a water manometer in the following manner.

The distance from the common duct to the surface of the abdomen averages 100 millimeters. If an intraductal pressure of 90 millimeters of water, measured directly with a water manometer causes a flow through the sphincter, then bile will flow through the sphincter spontaneously against a resistance of 90 millimeters water pressure rather than upwards through the biliary sinus of 100 millimeters water pressure. If therefore the sphincter possesses a tonus equivalent to 90 or less millimeters, removal of the "T" tube results in closure of the biliary sinus in almost exactly seven days.

Nothing is gained by leaving this foreign body in the common duct for long periods of time even in chronic cholangitis, if the sphincter tonus permits of a free flow of bile into the duodenum.

4. ANALYSIS OF FINDINGS and RESULTS

The following analysis embraces 106 patients with biliary tract disease consecutively admitted to and operated upon at Knickerbocker Hospital by eleven staff surgeons in the five year period between April 1937 and June 1942.

ADMISSIONS AND OPERATIONS BY MONTHS AND SEASONS

JANUARY	9	APRIL	14
FEBRUARY	9	MAY	8
MARCH	9	JUNE	15
WINTER	27	SPRING	37
JULY	5	OCTOBER	13
AUGUST	5	NOVEMBER	4
SEPTEMBER	7	DECEMBER	8
SUMMER	17	FALL	25

From these figures no clear seasonal relation is apparent. The highest incidence occurred in the spring months and the lowest in the summer months. The lower incidence in summer may be due to lack of respiratory infections, more active outdoor life and a tendency to eat less heavy, fatty foods.

S E X

In the series were 90 females and 16 males, a ratio of 5.6 females to one male. This is an unusual ratio for the males. No explanation is offered.

C O L O R

One hundred four patients were white to only two colored. The colored patients were both females. This dearth of colored females and absence of colored males is in conformity with the very low incidence of this disease even in the southland.

N A T I V I T Y

United States	52	South America	1
Puerto Rico	17	Russia	1
Ireland	13	Roumania	1
Germany	5	Scotland	1
England	2	Poland	1
Greece	2	Sweden	1
Denmark	2	France	1
Central America	1	Hungary	1
North Africa	1	West Indies	1
Santo Domingo	1	Venezuela	1

A glance at the nativity of these patients corroborates an earlier statement that they represent many nationalities. From these figures one is unable to state, however, that one nationality is more susceptible than another.

AGE RELATIONS

Extremes of Age 16 and 74 years
 Average Age of All Patients 42.04 years
 Average Age of Females (90) 40.47 years
 Average Age of Males (16) 48.12 years

The 16 year old and the 74 year old victims were females. The average age of the females at 40.47 is the usually accepted age for the occurrence of biliary tract disease in this sex. The male, however, is stricken at an average age of 8 years later in life, at the average age of 48.12 years. The youngest male patient was 35 years of age and the oldest 64 years.

INTERVAL BETWEEN FIRST ATTACK AND ADMISSION TO HOSPITAL

1 to 25 and more years	64 cases
1 to 10 months	20 cases
1 to 4 weeks	7 cases
1 to 10 days	15 cases

Over sixty percent of the cases had experienced disease from one to twenty-five and more years before admission to the hospital. Only 20% of the entire series gave a total history of one month or less. The remaining 20% had biliary tract disease for from one to ten months.

DURATION OF PRESENT ATTACK BEFORE ADMISSION TO THE HOSPITAL

5 to 17 hours	15 cases
1 to 10 days	58 cases
1 to 5 weeks	22 cases
1 to 7 months	11 cases

This tabulation shows that only 14.2% of the entire group of 106 patients presented themselves for treatment within the first 24 hours of the onset of the attack which was sufficiently severe to cause them to seek relief.

Fifty-eight patients or 55% of the series were ill of their hospitalizing attack between one and ten days before requesting admission, although the process in many was acute. Weeks and months elapsed in the remaining thirty-three patients between the beginning of their last attack and hospital admission. These figures demonstrate lucidly the difficulty of early operation in biliary tract disease.

PATIENT'S DESCRIPTION OF PAIN

"Sharp"	60	"Pain"	3
"Severe"	16	"Hunger"	1
"Colicky"	13	"Pressure"	1
"Stabbing"	4	"Soreness"	1
"Distension"	4	"Bloating"	1
"Gassy"	3	"Dull"	1

In the 60 patients describing their pain as "sharp" stones were present 49 times or in 81.7%. When it was declared "severe" in the 16 cases, lithiasis was present 15 times or in 93.8%. While when the pain was described as "colicky," calculi were present in only 9 out of 13 cases or 69.2%. Combining these figures it was found that stones were present somewhere in the biliary tract in 82% of instances when pain was described as "sharp," "severe" or colicky.

LOCATION OF PAIN

Right upper quadrant	53 cases
Epigastrium	30 cases
Right upper quadrant & epigastrium	13 cases
Upper abdomen	6 cases
Right lower quadrant	1 case
General abdomen	1 case
Right back	1 case
Both flanks	1 case

Stones were present 48 times or in 90.6% of the 53 cases in which the pain was located in the right upper quadrant. In the 30 instances of pain in the epigastrium, stones were found in 23 patients, an incidence of 76.7%. Pain, therefore, in either the epigastrium or right upper abdominal quadrant, in the presence of biliary tract disease presents the probability of the presence of stones in 85.5% of such cases, if any conclusion is justified by this analysis.

RADIATION OF PAIN & RELATION TO PRESENCE OF CALCULI

Radiation to	Total Cases	With		
		Without Stones	With Stones	% With Stones
No radiation	35	27	8	77.1%
Back	27	23	4	85.1%
Rt. scapula	17	16	1	94.1%
Rt. scapula & back	12	3	9	75.0%

Two cases each gave a history of radiation to (a) interscapular area, (b) right upper quadrant (c) right lower quadrant.

One case each gave a history of radiation to: (a) left upper quadrant and both scapulae, (b) left upper quadrant, (c) both lower quadrants, (d) back and interscapular area, (e) right upper quadrant and right scapula, (f) epigastrium and testes, (g) back and both scapulae, (h) both shoulders, (i) left upper quadrant and back.

Stones were present in 77% of 35 cases in which pain did not radiate.

Pain radiated to the back, right scapulae and simultaneously to the back and right scapula 27, 17 and 12 times respectively. Only in these instances of radiation was the number of cases sufficiently large to consider statistically. When the locus of radiation was the right scapula, the incidence of lithiasis was 94.1%. Calculus was present in 85.1% of cases when pain radiated directly through to the back while stones were present in only 75% in cases showing radiation concomitantly to the right shoulder and back. Therefore, according to these figures, calculous disease is more probably present when pain is radiated to the right scapula than to any other location.

According to the history obtained, pain was provoked by the taking of fatty foods in 50 or almost one-half of the cases.

Pain was relieved in only 7 patients by vomiting. Next to pain, vomiting was the second most con-

sistent manifestation. This occurred in 83 out of the 106 patients or in 78.3%.

Clinical jaundice was observed upon admission only twenty times. Jaundice was associated with acholic stools in only twelve of these twenty cases.

ICTERUS INDEX IN BILIARY TRACT DISEASE

CALCULOUS DISEASE

(Range 3.6% to 290%)

I. I. Determinations made in	71 cases
I. I. greater than 15% (jaundice)	29 cases
Percentage incidence of jaundice	40.8%

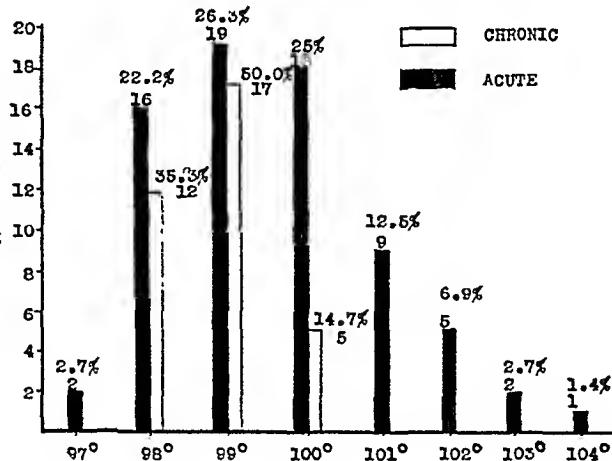
NON-CALCULOUS DISEASE

(Range 8.3% to 210%)

I. I. determinations made in	16 cases
I. I. greater than 15% (jaundice)	6 cases
Percentage incidence of jaundice	37.5%

Icterus index determinations were made upon 87 patients, and values of more than 15% were found 35 times. Jaundice, therefore, was present to the extent of 40.2%. Further scrutiny of these figures shows jaundice to be present to almost the same extent in non-calculus as in calculus disease.

RELATION OF TEMPERATURE TO ACUTE AND CHRONIC PROCESS



This graph depicts the relationship of the admission temperature to the acuteness or chronicity of the disease.

In the chronic cases the temperature ranged from 98° to slightly less than 100° farenheit. In no instance was it quite as high as 100° farenheit. In 50% of the temperature was between 99° and 100° farenheit.

Acute cases, however, were found throughout the temperature range from 97° to 104° while seventy-four percent of the acute cases were found to have admission temperatures between 98° and 100°. Only

about twenty-six had temperatures above 100°. These facts clearly demonstrate the utter lack of correlation between the height of temperature and the acuteness or chronicity of the disease.

An attempt at a correlation between the white blood cell and differential counts and the nature of the process was futile.

In both the acute and chronic cases the total white cell counts ranged irregularly between five and twenty-five thousand cells. The differential counts were found in both instances to vary inconsistently from 47% to 95% polymorphonuclear leucocytes. Therefore no conclusions were possible.

Nothing remarkable was revealed by the routine aerobic and anaerobic cultures of the liver, gall bladder wall and its contents, except the discovery of typhoid in the gall bladders of two cases. Subsequent follow-up of these two typhoid carriers, showed them to be cured.

Liver biopsies were taken in forty-one cases. In seventeen or 41.4% of the specimens, no morphological changes could be demonstrated.

Twenty-four or 58.6% of the specimens showed such morphological changes as: acute hepatitis, acute cholangitis, multiple abscesses, fatty metamorphosis of parenchymal cells, perihepatitis and pericholangitis. Such are the usual changes seen in association with biliary tract disease.

Among the more remarkable findings revealed in the liver biopsies were the occurrence of Schistosomiasis Mansoni in two cases and polyarteritis nodosa in a third case.

The gall bladders contained acute inflammatory changes in three of the seventeen instances, when the liver specimens revealed no disease. Chronic gall bladder inflammation was associated with the remaining fourteen normal liver specimens.

Normal liver morphology was present in the acute biliary tract disease six times and in the chronic form eleven times.

In sixteen of the seventeen cases showing no liver changes, lithiasis was present twelve times in the gall bladder, twice in the gall bladder and common duct, once in the cystic duct and once in the gall bladder, cystic and common ducts simultaneously.

Contrary to the ubiquitous statement that hepatitis is always associated with gall bladder disease, it is evident from these findings that biliary tract disease and not merely gall bladder disease not only can be but actually is present without associated pathological changes in the liver.

OPERATIONS PERFORMED BY SURGICAL STAFF

Surgeons	No. of Cases	Hospital Deaths	Percentage Mortality
11	106	6	5.66%

The series of 106 consecutive cases of biliary tract disease were operated upon by eleven staff surgeons.

A total of six patients died, a mortality of 5.66% in contrast to that of approximately 15% in the previous five year period.

Analysis of 106 Consecutive Operations on the Biliary Tract 1937-1942

Operation	Total No.	Mortality No.	Mortality Percent
Chronic Disease			
Cholecystectomy	34		
Alone	20		
With Appendectomy	5		
With Dochootomy	7	1	14.3%
With Dochotomy	1		
With Dochotomy and other operations	1		
Total Chronic Disease	34	1	2.9%
Acute Disease			
Cholecystectomy	66	4	6.0%
Alone	33	2	6.1%
With Appendectomy	15		
With Dochootomy	8	1	12.5%
With Dochotomy	5	1	20.0%
With Other Operations	5		
Cholecystostomy	6	1	16.6%
Alone	4		
With Dochotomy	1		
Cholecyst-Jejunostomy	1	1	100.0%
Total Acute Disease	72	5	6.94%
Total for All Operations	106	6	5.66%

This chart shows a hospital mortality of 2.9% in 34 cases of chronic biliary tract disease, the single death following choledochostomy associated with cholecystectomy.

In the 72 cases of acute biliary tract disease, five patients died, yielding a hospital mortality for this more hazardous group of 6.94%. This figure by comparison with that from some other sources, is still high by approximately 3%. In defense, it might be stated that at least two of these patients presented no alternative but to be operated upon in the face of an almost fatal cholemia upon admission. The icterus index was 210% in one and 290% in the other. Eliminating these two cases, the mortality in the acute group becomes 4.2% and for the entire series of 106 cases 3.77%.

CAUSE OF DEATH

Name	Diagnosis	Cause of Death
F.N.	Calculous Choledochal	Surgical Shock
57	Obstruction	Cholemia (I.I.290)
F.		
J.P.	Perforation of Gangrenous	Surgical Shock
71	Empyemic Gall Bladder	
F.	Pericholecytic Abscess	
	Cholodocholithiasis	
R.W.	Acute Calculous	Hemorrhagic Shock
30	Gall Bladder Disease	
F.		
E.G.	Chronic Biliary Tract Disease	Pulmonary Embolism
44	Calculi of Gall Bladder	
F.	Cystic and Common Ducts	
	Choledochus Fistula	
Q.S.	Acute Exacerbation of Chronic	Acute Diffuse Peritonitis
43	Biliary Tract Disease. Calculi	Disseminated Foci of Liver Abscesses
F.	of Gall Bladder and Common Duct.	Acute Cholangitis
J.M.	Common Duct Obstruction	Acute Hepatitis and Hepatitis
64	Cholemia	Cholemia (I.I.210)
M.		Extensive Broncho-Pneumonia

In the six mortalities, surgical shock occurred twice as the precipitating cause of death. Both patients were in the upper age group and were critically ill before operation. Hemorrhagic shock accounted for another death. This case demonstrates one of the possible hazards of cholecystectomy in the acute state of biliary tract inflammation a hazard that should always be anticipated.

Pulmonary embolism, acute diffuse peritonitis and diffuse, pan-hepato—biliary inflammation and bronchopneumonia were the causes of death in the remaining three mortalities of the series.

Ninety-five cases were drained with one or more drains consisting of: penrose, dakin tubes, catheters and the long arm of "T" tubes.

Of the 11 cases closed tightly, two died, bile peritonitis contributing to the mortality in one of them. The presence of bile in the peritoneum escaped clinical detection. The presence of a drain or diagnostic paracentesis might have prevented this fatality.

The upper right rectus longitudinal incision was used 86 times to 20 times for the subcostal or oblique incision.

There were no hospital eviscerations, although dehiscence occurred in two longitudinal incisions. Up to the time of discharge from the hospital there were no incisional herniae nor weakness in the incision.

Of the 106 cases operated upon, three died within 24 hours after operation. Of the 103 remaining cases only two became infected at elsewhere than the site of the drain, a percentage of 1.94. These cases, however, are all considered borderline or potentially infected rather than clean cases becoming infected.

PERIOD OF HOSPITALIZATION

The average preoperative residence was 6.9 days. The postoperative stay was 18.2 days, making the total hospitalization 25.1 days. This rather prolonged hospital residence was contributed to by three cases that remained for 58, 57 and 54 days each. One case was typhoid cholecystitis, the second a very severe liver abscess complicating the biliary tract disease, and the third case was one of advanced liepato-cholangitis.

DIAGNOSIS OF ACUTE CASES

Criteria for Determination of Acute Cases

By Clinical, Operative and Pathology

Study Combined	22 cases
By Pathology Alone	14 cases
By Clinical Criteria Alone	12 cases
By Operation Alone	5 cases
By Operation and Clinical Criteria	6 cases
By Operation and Pathology	7 cases
By Clinical and Pathology Criteria	6 cases
Total	72 cases

In arriving at a diagnosis of acute biliary tract disease, three criteria were used. The first is similar to

that postulated by Pennoyer for acute cholecystitis namely; that on admission the patient have three or all of the following findings; (Pennoyer specifies all four) (a) severe pain in the gall bladder region, (b) definite muscle spasm and local tenderness in the right upper quadrant, (c) rectal temperatures of 101 or over and (d) leucocytosis of 12,000 or over. The second means of arriving at the diagnosis was the microscopic study by the pathologist; lastly, the diagnosis was made by the surgeon at the time of operation. Any one or combination of these diagnoses caused the case to be classified as acute.

The great disadvantage of such a method of classification is that it cannot be arrived at preoperatively. It is, however, of interest to note that the pre-operative clinical diagnosis was in agreement in 46 out of 72 cases or 70%. This is the identical figure obtained at the Mayo Clinic for their 1941 series of 1335 cases.

Distribution of Stones in the Series of 106 Cases.

Chronic Series

Chronic Biliary Tract Disease	34 cases
Chronic Biliary Tract Disease without Stones	3 cases
Chronic Biliary Tract Disease with Stones	31 cases
<i>Location of Stones:</i>	
Gall Bladder	21 cases
Cystic Duct	3 cases
Common Duct	1 case
Gall Bladder and Cystic Duct	1 case
Gall Bladder and Common Duct	2 cases
Gall Bladder and Cystic and Common Duct	3 cases
Percentage of Chronic Cases with Stones	91.2%
Percentage Chronic Cases without Stones	8.8%

Acute Series

Acute Biliary Tract Disease	72 cases
Acute Biliary Tract Disease without Stones	15 cases
Acute Biliary Tract Disease with Stones	57 cases
<i>Location of Stones:</i>	
Gall Bladder	37 cases
Cystic Duct	7 cases
Common Duct	1 case
Gall Bladder and Cystic Duct	5 cases
Gall Bladder and Common Duct	6 cases
Gall Bladder and Cystic and Common Ducts	1 case
Percentage Acute Cases with Stones	80%
Percentage Acute Cases without Stones	20%
Percentage Total Cases with Stones (106)	83%

In this series of 106 consecutive cases, 34 were chronic and 72 were acute. Stones were present in 31 of the 34 chronic cases or 91.2%. Calculi were present 57 times in the 72 acute cases or in 80%. Concretions then were present in 88 patients or 83% of the entire series.

Lithiasis was distributed as follows: 58 times in the gall bladder alone; 10 times in the cystic duct alone; twice in the common duct alone; six times in the gall bladder and cystic duct; eight times in the gall bladder and common duct, and four times in the gall bladder, cystic and common duct simultaneously.

In this series, contrary to reports from most sources, the incidence of stones in the chronic disease at 91.2% is higher than that in the acute series, at 80%.

ANALYSIS OF ACUTE CASES

Total Acute Biliary Tract Disease	72 cases
Percentage Acute Cases in Series	68%
Perforation in Acute Cases	3 cases
Percentage Perforation in Whole Series	2.8%
Percentage Perforation Acute Cases	4.2%
Gangrenous Gall Bladder	1 case
Percentage Gangrenous in Whole Series	0.94%
Percentage Gangrenous Acute Cases	1.4%
Number Acute Cases with Stones	57 cases
Percentage Acute Cases with Stones	80%
Mortality of Acute Cases	5 cases
Percentage Mortality of Acute Cases	6.9%
Mortality Perforated and Gangrenous Cases	0

In the 72 acute cases of biliary tract disease, gall bladder perforation occurred three times or in 4.2%. Gangrene of the gall bladder was reported once or in 1.4% of the acute series. It is interesting to note that none of these four patients died. Five of the 72 acute cases died—a mortality of 6.9%.

Time of Operation

Acute Cases Operated During First Six Days	—30 cases
1st Hospital Day	3 cases
2nd Hospital Day	4 cases
3rd Hospital Day	2 cases
4th Hospital Day	6 cases
5th Hospital Day	5 cases
6th Hospital Day	10 cases
Deaths in Acute Cases Operated During First Six Days	
During First Six Days	2 cases
5th Hospital Day	1 case
6th Hospital Day	1 case

Time of Operation

Acute Cases Operated After 6th Hospital Day	—42 cases
7th Hospital Day	6 cases
8th Hospital Day	5 cases
9th Hospital Day	6 cases
10th Hospital Day	5 cases
11th Hospital Day	5 cases
12th Hospital Day	5 cases
13th Hospital Day	4 cases
14th Hospital Day	4 cases
21st Hospital Day	1 case
22nd Hospital Day	1 case
32nd Hospital Day	1 case
Deaths in Acute Cases Operated After 6th Hospital Day	
3 cases	
7th Hospital Day	1 case
9th Hospital Day	1 case
32nd Hospital Day	1 case

Two of the mortalities occurred in a group of 30 cases that were operated upon during the first six days after admission. One of the fatal cases was operated on the fifth day and the other on the sixth hospital day. The remaining three deaths occurred among the other 42 patients operated upon between the 7th and 32nd hospital day. The preoperative hospital days for these three cases were 6, 9 and 32 days. No mortalities therefore were experienced in those cases operated upon prior to the fifth hospital day.

The duration of the attack resulting in and antedating admission in these five fatal cases were: one day, two days, five days, four weeks (with silent jaundice) and four weeks.

The weight of evidence from many clinics, as well as this service, is overwhelmingly in favor of operation within forty-eight hours of the onset of the acute attack. However, one of the primary difficulties is the impossibility to ascertain the time of the transition of the chronic state into the acute process. As stated previously, 30% of the acute cases go unrecognized until confirmed by celiotomy or microscopic examination. Three of the five fatalities in this acute series were not classified as such, preoperatively. In many instances the condition has advanced to the state where supportive measures rather than surgery are indicated.

The practice at Knickerbocker Hospital is to individualize each case. While the infusion of glucose, fluids and other necessary preoperative measures are being executed, careful and frequent observations of the patient are made. Failure particularly of subsidence of pain and pulse within 12 hours after hospitalization, are two important indications for immediate surgical intervention, since perforation has occurred or is imminent. Immediate surgery has been resorted to because of this, in a very small group.

There is an equally small group of patients who although acute upon admission, are critical because of persistent and progressive cholelithiasis, circulatory incompetency, etc. Immediate surgery while indicated must of necessity be delayed.

The largest group, probably comprises two components. One improves almost immediately upon hospitalization, while the other shows the same "cooling off" or improvement after two days of hospitalization.

In the first instance the acute phase was probably subsiding at the time of admission, while in the other the acute inflammatory phase subsided within the first two days of rest and treatment in the hospital.

Calculi were present in four of the five fatal acute cases. In three of these, stones were found in the common duct.

The relative incidence of acute biliary tract disease between females and males is 3.8 to 1 as compared to 5.6 females to 1 male for the entire series. The mortality ratio was 4 females to 1 male.

AGE OF ACUTE CASES

Average Age in Entire Series (106 cases)	42.0 years
Average Age in 72 cases—Acute	48.1 "
Average Age in 15 Males—Acute	49.2 "
Average Age in 57 Females—Acute	40.1 "
Average Age in 5 Fatal Acute Cases	53.0 "

The average age for the entire series was 42 years while that in the acute series of 72 cases was 48.1 years.

The 15 males at 49.2 years were nine years older than the 57 females at 40.1 years when stricken with acute biliary tract disease.

The average age in the five fatal cases was 53 years.

Disregarding all other causes of death, an increase of ten years over middle-age (45) is an important factor in the mortality rate of any major surgical procedure.

Before attempting a summary of the results herewith presented, a few pertinent remarks seem to be in order.

A serious attempt was made upon admission to thoroughly evaluate the physiological status of the patient as well as to determine as correctly as possible the degree of emergency for surgery. The dominant motive in this effort was to intervene surgically at the most optimum time if no emergency existed.

In those cases of peritonitis from perforation or when this condition seemed imminent, surgery was performed after only a very short period of fluid and electrolyte replacement. While regrettable, there are cases in which this catastrophe occurs several days prior to admission and consequently there is no longer an optimum period in which to operate after arrival at the hospital. The problem in these cases is not whether to operate early in the course of the disease or to delay operation, but rather that of physiological rehabilitation to withstand the indicated surgical procedure. Two such unfortunate episodes occurred in this series, resulting in fatalities which were anticipated preoperatively because of irretrievable physiological incompetence.

In the major group which were not considered emergency cases, they were given the advantage of thorough preoperative preparation, complete diagnostic work-up, and medical consultation, if indicated. In cases where anaesthesia difficulty was anticipated before operation, the director of anaesthesia examined the patient and outlined the agent and technique to be employed.

Throughout this period there has been wholehearted co-operation by the attending and house staffs as well as by all of the associated departments in the hospital.

In a comparison of these results with those in a previous similar period, great advantage has accrued in terms of morbidity and mortality and also in the knowledge gained by all who have been associated in the project.

In considering this entire report involving one hundred and six consecutive cases of biliary tract disease, the following conclusions seem justified.

CONCLUSIONS

(1) Although not a seasonal malady the incidence of this disease is highest in first the spring and next highest in the winter months. Respiratory infections, heavier food and lack of exercise are suggested etiological associations.

(2) 5.6 times as many females as males were afflicted. This is an unusually high proportion of females.

(3) Two colored patients to 104 whites, again demonstrates the low incidence of biliary tract disease in the negro.

(4) In this relatively small series, twenty nationalities are included.

(5) This disease crystallized in the female at the age of 40.47 and eight years later in the male at 48.12 years.

(6) 61.5% of the series gave a history of symptoms from one to twenty-five and more years. In the remainder, symptoms started one day to ten months prior to entering the hospital.

(7) The interval between the start of the present attack and hospitalization varied from one to ten days in 55% of the series, and less than twenty-four hours in only 14.2% of the cases. In the remaining 30%, weeks and months elapsed.

(8) In 82% of the patients describing their pains as "sharp," "colicky" or "severe," calculi were found in some part of the biliary tract.

(9) Biliary tract concretions were present in 90.6% when pain was located in the right upper quadrant and present in 76.7% of patients with biliary tract disease with pain in the epigastrium.

(10) Stones were present in 94.1% of cases when pain was radiated to the right scapula and in 85.1% when radiated directly posteriorly to the back. On the contrary stones were present in 77% of patients in whom there was no radiation of pain.

(11) Vomiting was the most consistent symptomatic manifestation it being present in 78.3% of cases. However, pain was relieved by vomiting in only seven instances.

(12) Clinical jaundice was observed twenty times upon admission. In twelve of these cases it was associated with acholic stools.

(13) The icterus index was greater than 15% in 40.8% of the cases with calculous disease and in 37.5% of those without calculi. Jaundice therefore is present in noncalculous disease almost as frequently as in calculous disease.

(14) Rectal temperature in the chronic cases ranged from 98° Farenheit to slightly less than 100°. No chronic case had a temperature as high as 100° Farenheit.

(15) Seventy-four percent of acute sufferers showed a temperature range of 98° to 100° Farenheit. The remaining twenty-six percent ranged between 97° and 104° Farenheit.

(16) No relation was found between the differential blood count and the acuteness or chronicity of the disease process.

(17) Culture of liver specimens, gall bladder wall and its contents, typhoid bacilli were found in two instances. No other remarkable findings were revealed by aerobic or anaerobic cultures.

(18) Liver biopsy was performed forty-one times in the 106 cases. In seventeen or 41.4% of the specimens removed no morphological changes were observed.

Liver specimens were entirely normal six times when associated with acute biliary tract disease and eleven times in chronic biliary tract disease.

Among the more remarkable findings revealed by the liver biopsies were the occurrence of SchistosomiasisMansonii in two instances and periarteritis nodosa in a third case.

(19) Ectomy was performed in 34 chronic cases with one death, a percentage of 2.9%. Ectomy was performed in 66 or 72 acute cases with 4 deaths or 6% mortality. Ostomy of the gall bladder was the opera-

tion in six of the acute cases, one died giving a mortality of 16.6%.

In the entire series of 106 cases of acute and chronic cases combined, there was a hospital mortality of 5.66% due to a total of six deaths.

(20) The six mortalities were caused by; surgical shock in two; hemorrhagic shock in one; pulmonary embolism in one; diffuse peritonitis in one and severe pan-hepato-biliary inflammation in one.

(21) All cases were drained except eleven, bile peritonitis contributing to the death of one of these patients.

(22) No herniae eventuated in the eighty-six upper right rectus, longitudinal or the twenty oblique, subcostal incisions.

There were no eviscerations, however, dehiscence occurred twice in upper right rectus incisions.

(23) Only two incisions became infected, elsewhere than at the site of the drain, a percentage of 1.94, although all cases were considered potentially infected.

(24) The average total hospital residence was 25.1 days composed of 6.9 preoperative and 18.2 postoperative days. Three cases were in residence 58, 57 and 54 days each.

(25) The diagnosis in the seventy-two acute and thirty-four chronic cases was based on specified clinical findings, morphological study and surgical diagnosis individually and combined. By this method of classification the preoperative clinical diagnosis was found to be correct in 70% of the acute series.

(26) Stones were present in 91.2% of the chronic and 80% of the acute cases of biliary tract disease.

(27) Perforation of the gall bladder was present in three or 4.2% of the acute series and gangrene in one

case or 1.4%. All of these patients survived.

(28) The five fatal patients in the acute series were operated upon after the fourth hospital day. Three of these patients had their final attack a minimum of five days before admission.

(29) Common duct calculi were present in three of the five fatal acute cases.

(30) The female to male ratio in the entire series of 106 cases was 5.6 to 1, while in the acute series of 72 cases it was reduced to 3.8 females to one male. One male and four females succumbed.

(31) The average age at which operation was performed in the combined acute and chronic groups was 42 years, and in the acute group 48.1 years.

The fifty-seven females in the acute series averaged 40.1 years of age in contrast to 49.2 years of age in the fifteen males.

The average age in the five fatal acute cases was 53 years.

Disregarding all other causes of death, an increase of ten years beyond middle age is an important factor in the mortality rate of any major surgical procedure.

In conclusion, it is felt that adherence to such a comprehensive, supervised routine decreased the period of hospitalization by accelerating the pre, co and post surgical phases of these patients with biliary tract disease.

Secondly, clinical acumen on the part of both the house and attending staffs was sharpened, which resulted in more accurate diagnoses and precise evaluation of the physiological status of the patient. And, finally, surgical judgment was forced by a spirit of rivalry to become more circumspect.

All of these factors operating simultaneously lowered the hospital mortality at least sixty percent in this five year period.

Glossitis and Cheilosis Healed Following the Use of Calcium Pantothenate

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SINCE it has been recognized that vitamin deficiency states have been relatively common among our population and that they may be of great clinical importance without all of the manifestations of the classic disease pictures, the appearance of the tongue has regained significance in medical diagnosis. One of us (1) has described some of the lesser manifestations of pellagrous glossitis which may not all be entirely due to nicotinic acid deficiency. The role of deficiency of factors of the Vitamin B complex, other than nicotinic acid, in the causation of glossitis has subsequently been reported.

Garcia (2) has reported the occurrence, in Spain during the civil war of 1936 to 1939, of large numbers of cases of varying severity of "simple glossitis," which commonly were not accompanied by other manifestations of pellagra. These varied from hypertrophy of papillae with inflammation of the tip and sides of the tongue to denudation of the mucosa with complete papillary atrophy of the anterior portion of the tongue, congestion and ulceration of the buccal mucosa, pain and salivation. The glossitis was uninfluenced by treatment with vitamins A, D, C, B₁ or riboflavin. It was only partially improved by nicotinic acid—chiefly relief of pain. It was relieved by yeast and by liver extract.

Kruse, Sydenstricker, Sebrell and Cleckley (3) reported a glossitis which was observed in subjects on a basal diet supplemented with thiamine, nicotinic acid, ascorbic acid and cod-liver oil. The tongue was de-

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scribed as clean with flattened or mushroom shaped papillae and of a purplish red or magenta color. The glossitis was reported to have cleared after the administration of riboflavin and to have recurred upon the withdrawal of riboflavin.

Rosenblum and Jolliffe (4) reported "a number" of patients with frank nicotinic acid and riboflavin deficiency in whom, after treatment with nicotinic acid and riboflavin, the tongue was smooth, slightly edematous and of a peculiar purplish or magenta hue. These patients often complained of pain in the tongue. The tongue returned to normal after treatment with the whole vitamin B complex. In one case such a glossitis, which developed while receiving a basal diet supplemented with nicotinic acid, thiamine, ascorbic and vitamin A, was relieved after treatment with pyridoxine.

Vilter, Bean and Spies (5) reported the healing of ulceration of the tongue and relief of burning sensations of the mucous membranes in pellagrins following the administration of adenylic acid, although the fiery red color of the glossitis was not affected.

Cheirosis, the most common manifestation of which is a maceration or even an ulceration at the angles of the lips, with maceration extending outward over the skin, was described by Stannus as occurring in pellagrous prisoners in Nyasaland (6) and subsequently (7) quoted by him as having been described by early pellagrologists. Sebrell and Butler (8) reported its development in subjects on a pellagra producing diet supplemented with cod-liver oil, thiamine and ascorbic acid, and its healing during treatment with riboflavin after it had not healed during nicotinic acid therapy. Smith and Martin (9) reported the healing of cheirosis during supplementation with pyridoxine hydrochloride alone in three cases—in one while on a diet deficient in riboflavin and in another whose previous diet was considered adequate in riboflavin. In a fourth case, cheirosis was not healed by treatment with both pyridoxine and riboflavin but did heal following the administration of large doses of parenteral, refined and concentrated liver extract.

Machella (10) reported the failure of healing of cheirosis with riboflavin in 8 patients; the healing of cheirosis in 9 of 13 cases during treatment with pyridoxine, 2 of whom had not healed during riboflavin therapy; the healing of cheirosis in 2 cases during supplementation with yeast after failure of healing with both riboflavin and pyridoxine; the healing of cheirosis during the administration of ascorbic acid in 3 cases, 2 of whom had not healed during treatment with riboflavin (relatively small doses in 1 case) plus nicotinic acid in 1 case and pyridoxine in the other; and the healing of cheirosis during treatment with nicotinic acid in 2 cases, one of whom had not healed during treatment with riboflavin and pyridoxine, the other after no previous supplementation.

It is the purpose of this paper to report some instances of glossitis which developed during or persisted following the administration of nicotinic acid and some other members of the vitamin B complex and which have been relieved following the administration of calcium pantothenate. In one of them, cheirosis was also

present and did not heal until calcium pantothenate was given.

Case No. 1, J.E.B., a 79 year old retired banker with generalized arteriosclerosis and Parkinsonism had had, during convalescence from mild bronchopneumonia, two years previous, periods of agitation, hallucinations, and delusions. His tongue was bright red and atrophic and his legs scaly. His main meal was breakfast which consisted largely of carbohydrate foods. Other meals were qualitatively good but only small portions were taken. During treatment with capsules containing liver extract fortified especially with nicotinamide he made a good recovery and was able to carry on his usual limited activity, taking 2 of the vitamin B complex capsules daily.

In July, 1941, it was noted that his tongue was again atrophic and a deep rather than a scarlet red. He was again having episodes of milder agitation, hallucinations and delusions. He was given extra supplements of thiamine chloride by mouth, 15 mg. daily for one week and 1 mg. daily thereafter. He was also given consecutively during three two week periods, divided daily oral doses of 450 mg. nicotinamide, 12 mg. of riboflavin and 150 mg. of pyridoxine hydrochloride without any change in the appearance of the tongue. Subsequently, during treatment with 150 mg. of calcium pantothenate daily, by mouth, the color of the tongue became decidedly lighter after one week, and normal after two weeks. There was beginning regeneration of papillae after two weeks and this was considered to be complete after six weeks.

SUMMARY—A man who was receiving vitamin B complex capsules to supplement an inadequate diet after a psychosis, thought to be pellagrous, developed a glossitis which was not changed by extra supplements of thiamine, nicotinic acid, riboflavin and pyridoxine. The tongue became normal in appearance when calcium pantothenate was given.

Case No. 2, M.B., a 61 year old housewife was admitted to the hospital on October 6, 1941, with a diagnosis of subsiding acute cholecystitis. Her diet had been inadequate for many years. She had had intermittent attacks of gallbladder disease for five years, during which times her diet was worse, particularly during the previous two weeks of illness.

She was febrile, somewhat irrational and delirious. The skin was not abnormal. The tip of the tongue was red and smooth. The tendon reflexes of the legs were diminished but present. There was no calf tenderness. She remained quite ill with abdominal pain and daily fever of 102° to 103°. She continued to be irrational at times. She was given a liquid and soft diet, as tolerated.

After 10 days it was noted that her tongue had become fiery red and denuded of papillae. It was not sore. After 10 days of treatment with nicotinamide, 300 mg. daily, by mouth, the tongue was unchanged although her mental status was improved. The nicotinamide was then discontinued and she was given calcium pantothenate, 150 mg. daily, by mouth. The

following day the tongue appeared less red. After a week the color was nearly normal and it was thought that beginning regeneration of papillae could be seen. After three weeks of treatment with calcium pantothenate the tongue appeared normal except for slight redness and incomplete regeneration of papilla at the very tip.

SUMMARY—A woman whose diet had been inadequate for many years developed a pellagrous type of glossitis under observation when a recurrence of acute cholecystitis imposed a further limitation of diet. The glossitis remained unchanged during treatment with nicotinamide but improved rapidly when calcium pantothenate was given.

Case No. 3, F.I., a 67 year old housekeeper was admitted to the hospital on February 20, 1942 because of a generalized erythroderma, considered to be a contact dermatitis. She also had a large ulcer on her right leg which had recurred persistently following trauma 35 years previous. On the second day of hospitalization she became febrile and developed a pneumonitis, which was severe and persistent enough that she was in an oxygen tent for 25 days.

On the fourteenth day of hospitalization it was noted that her tongue, which had previously been normal, was scarlet red, uncoated and devoid of papillae. During the next 16 days she was given, intramuscularly, an experimental solution of vitamin B complex factors which provided an average daily dose of 562.5 mg. of nicotinamide, 16.9 mg. of riboflavin, 11.2 mg. of pyridoxine hydrochloride and 25 mg. of thiamine chloride. The solution of vitamins had originally contained calcium pantothenate also but it could not subsequently be identified in the solution. She also received ascorbic acid, averaging 200 mg. daily.

After three days of this treatment the tongue became a darker red. During the next 13 days of parenteral vitamin treatment and during the following 8 days in which she received 12 mg. of riboflavin daily by mouth, there was no further change in the appearance of the tongue.

She was given 150 mg. of calcium pantothenate daily, by mouth. Nine days later, when she was discharged from the hospital, the tongue was less red and there was apparent a beginning regeneration of papillae. She was given, for treatment at home, powdered oral liver extract, 12 gms. daily. Two weeks later her tongue was still slightly redder than normal near its tip. Regeneration of papillae had continued and they were estimated to be about one-half normal size.

The patient was readmitted February 1, 1944 because the ulcer on the right leg had extended, had become multiple and had an appearance suggestive of gummatous ulceration. A biopsy from the edge of an ulcer was compatible with but not diagnostic of a long-standing ulcerating gumma. On the first admission the first Kahn reaction had been doubtful, the second positive (3 units), and 4 others had been negative. The failure of healing then had been attributed to cicatricial obstruction to circulation. On the last admission the Kahn reaction was positive (20 units). Her

dietary history was not reliable but some of her remarks indicated that her diet had not been optimal and there had been frequent periods of vomiting of from one to several days, which were not explained by x-ray or spinal fluid examinations, during which times the limited food intake was chiefly bread and milk.

The tongue at the last admission was devoid of papillae but was only moderately reddened. Its surface was somewhat irregular and the possibility of luetic glossitis was considered. She was placed on a basal diet low in the vitamin B complex and given HgCl₂, KI and bismuth therapy. On the eighteenth day the tongue had become quite smooth, thin and scarlet red. She was then given a preparation containing 4.5 mg. of thiamine chloride and 270 mg. of nicotinic acid, divided into 6 oral doses, daily.

After 12 days of this treatment, the tongue had a somewhat darker red color but was otherwise unchanged in appearance.

The thiamine and nicotinic acid were then discontinued and she was given calcium pantothenate, 300 mg. in 3 oral doses daily. On the fourth day of this treatment the color of the tongue had receded considerably. On the ninth day the color was nearly normal and there was beginning regeneration of papillae.

SUMMARY—On the first admission, a glossitis which developed during the course of a prolonged pneumonia, was changed only by some deepening of color during large parenteral dosage with nicotinamide, thiamine, riboflavin and pyridoxine, for 16 days. After 9 days of treatment with calcium pantothenate there was improvement in color and beginning regeneration of papillae which progressed to an early normal appearance of the tongue after 2 weeks treatment with powdered oral liver extract after discharge from the hospital.

On the last admission, a possible luetic glossitis changed to a pellagrous glossitis after 17 days of antiluetic therapy and a diet limited in the vitamin B complex. Then, after 12 days of treatment with thiamine and nicotinic acid, the only change in the tongue was a somewhat darker red color. After 9 days of treatment with calcium pantothenate the color of the tongue was nearly normal and there was beginning regeneration of papillae.

Case No. 4, I.S., a 51 year old housewife was admitted to the hospital on February 27, 1943 with marked obesity (345 pounds, including a lot of edema), possible mitral insufficiency, a moderate hypertension and severe cardiac decompensation.

In addition to intensive cardiac therapy, she was placed on an 800 calory reduction diet. Supplements of 30 gms. of brewer's yeast daily were taken for three days and were then refused. She was given a preparation containing 1.5 mg. of thiamine chloride and 90 mg. of nicotinic acid daily.

On the 42nd hospital day it was noted that the tongue, which had previously been considered normal, had a deep purplish red color which was thought to have been partly due to cyanosis. There were multiple small fissures which gave it a somewhat lobulated

appearance but there was apparently complete atrophy of all papillae. 12 mg. of riboflavin daily by mouth, was added to the previous supplementation. After 12 days there was no change in the appearance of the tongue.

The riboflavin was then discontinued and 150 mg. of calcium pantothenate was given daily, by mouth. Five days later the color of the tongue had faded considerably. After another 8 days there was only a slightly abnormal redness of the tongue and beginning regeneration of papillae was apparent. Regeneration of papillae continued rapidly and was nearly complete when she was discharged from the hospital after another 11 days.

SUMMARY—Glossitis developed in a very obese woman on a strict reduction diet supplemented with good amounts of thiamine and nicotinic acid. It was not changed during 12 days of treatment with 12 mgs. of riboflavin daily. It improved to a nearly normal condition after riboflavin supplementation was replaced with calcium pantothenate.

Case No. 5, G.M.K., a 20 year old woman was admitted to the hospital on March 14, 1943 after 14 months of diarrhea, frequently bloody, due to ulcerative colitis. Because of a history of allergy in her past and in her family, she was placed on an elimination diet. This was supplemented with multiple vitamin capsules which furnished a daily dose of 4.5 mg. of thiamine chloride, 3 mg. of riboflavin, 0.75 mg. of pyridoxine, 3 mg. of calcium pantothenate, and 30 mg. of nicotinamide, except for a period from the 8th to the 20th hospital days when all medication was withheld. On the 47th hospital day she began to receive 8 gms. of succinyl sulfathiazole daily, to which was added, on the 63rd hospital day, 2 gms. of sulfadiazine daily. During this time she was usually having from 6 to 12 stools daily.

On the 80th hospital day there was noted a considerable bright redness of the anterior third and sides of the tongue, and a cheilosis at the corners of the lips. She was then given, in addition to the multiple vitamin capsules, 2 mg. of riboflavin and 200 mg. of nicotinamide, intramuscularly or intravenously, 2 or (usually) 3 times a day.

On the 89th hospital day there was no appreciable change in the appearance of the tongue or of the cheilosis. Pyridoxine hydrochloride, 25 mg. 3 times a day, intramuscularly, was then added to previous supplementation. After 3 days of this, the area of maceration at the corners of the mouth had decreased to about half of its original size. During the next 5 days the extent of the cheilosis fluctuated from day to day but was never estimated at less than one third of its original size. The tongue did not change in appearance during this time.

On the 95th hospital day parenteral doses of nicotinamide were discontinued. On the 97th hospital day calcium pantothenate, 100 mg. intramuscularly 3 times a day, was added to the parenteral doses of riboflavin and pyridoxine. Three days later the tongue appeared normal and the cheilosis had healed. The parenteral

vitamins were discontinued after 2 more days. The multiple vitamin capsules continued to be given orally. Three weeks later the tongue was again red over its anterior portion and there was again cheilosis at the corners of the mouth. This time the oral vitamin supplements were augmented only with calcium pantothenate, 100 mg. intramuscularly once or twice a day. After 4 days of this augmentation, the tongue again appeared normal and the cheilosis had healed.

SUMMARY—A girl with ulcerative colitis who was receiving a restricted diet, for the testing of allergic reactions, supplemented with multiple vitamin capsules, developed a glossitis and cheilosis. Neither lesions were changed during the parenteral administration of riboflavin and nicotinamide. The cheilosis improved but did not heal and the glossitis remained unchanged when pyridoxine was added to the parenteral vitamins. Both the glossitis and the cheilosis healed promptly when parenteral doses of calcium pantothenate were given. When the glossitis and the cheilosis reappeared, after the omission of parenteral vitamins, both lesions healed when parenteral doses of calcium pantothenate alone were given.

Case No. 6, F.H., a 66 year old unemployed lumberjack and road worker was admitted to the hospital on January 24, 1944 with orthopnea and anasarca, ascribed to arteriosclerotic and probably beriberi heart disease. There was a history of inadequate diet and alcoholism. He had a chronic pellagrous dermatitis with pigmentation, pustulation and ulcerations. His tongue was smooth, uncoated, devoid of papillae and of a deep purplish color, thought to be contributed to by cyanosis.

In addition to vigorous cardiac therapy, he was given thiamine chloride by mouth, 30 mg. daily for 10 days, followed by 1.5 mg. daily for the period of observation. He was given 600 mg. of nicotinamide by mouth daily for 41 days. On the 16th hospital day the tongue showed no change other than a brighter red color, presumed to be due to a decrease in cyanosis. Riboflavin was then given, 18 mg. daily, by mouth until the 40th hospital day. During this time there was no evidence of regeneration of papillae and the tongue became a still brighter red—almost scarlet.

On the 37th hospital day, calcium pantothenate was started, 300 mg. daily, by mouth. After 5 days there was a decided decrease in the redness of the tongue. After 9 days the tongue was approximately normal in color and beginning regeneration of papillae was apparent.

SUMMARY—The glossitis in a badly decompensated cardiac, which was pellagrous in type except for a deep purplish color, thought to be contributed to by cyanosis, was not changed during 36 days of treatment except to become a nearly scarlet red as he became compensated.

Large doses of thiamine and nicotinamide were given at first. To these were added large doses of riboflavin for 24 days. When calcium pantothenate was given the color of the tongue became approximately normal and beginning regeneration of papillae was apparent.

COMMENT

These patients either gave histories of having taken inadequate diets by neglect or they had conditions which prevented the intake of a normal diet or its proper utilization (ulcerative colitis).

It would appear from these observations that it is possible for one to receive an inadequate supply of pantothenic acid, or to utilize it inadequately, despite its wide distribution in nature. It seems that in these cases the healing of glossitis and cheilosis may, with fair certainty, be ascribed to treatment with calcium pantothenate, particularly in case 5 in which the lesions recurred and were then treated only with calcium pantothenate. In the others, the supplements of other fractions of the vitamin B complex were given in large enough doses for long enough periods of time so that a therapeutic effect should have been obtained from them. Cases No. 3 (last admission), 4, and 5 were on controlled diets. There was no significant change in the diet of Case No. 1 during the period of observation of the glossitis. The periods of observation of the effects of the separate fractions of the vitamin B complex prolonged the hospitalizations so that the patients were kept under observation long enough for a complete restoration to normal appearances to be seen only in cases 1 and 5. In cases 2, 3 (after the first hospitalization), and 4 there was a close approach to normal appearance during the periods of observation. In cases 3 (last admission) and 6, it can only be said that the color of the tongues was restored to approximately normal and that there appeared to be a beginning regeneration of papillae.

It may be presumed that vitamins which are essential

for experimental animals are also essential for man. It is of interest, in view of the neurological lesions which develop in experimental animals deprived of pantothenic acid (11), that no definite neurological lesions were noted in these patients except for case 1. In that case, it is difficult to separate the effects of senile changes from those of nutritional deficiency. The first episode of psychosis seemed, at the time, to be of pellagraous nature.

The glossitis in these patients, which was relieved by calcium pantothenate after failure of other fractions of the vitamin B complex, was characterized by atrophy of all papillae, absence of coat, and a slightly purplish redness which was darker than the scarlet red of nicotinic acid deficiency glossitis except in cases 2, 5 and 6. In these cases, after large doses of niacinamide and (except in case 2) riboflavin, the tongue might well have been described as scarlet red.

Like Smith and Martin (9) and Machella (10), we have seen a number of cases of cheilosis which did not heal after large doses of riboflavin. Case 5 of this series is the only one of them which subsequently failed to heal when given pyridoxine. It is of interest, but not necessarily surprising, that different vitamins should be necessary for the prevention or cure of apparently identical lesions. It seems that pantothenic acid must be added to the list of vitamins necessary for the prevention or cure of cheilosis.

SUMMARY—Six cases of glossitis and one of cheilosis have healed completely or shown good progress toward healing during treatment with calcium pantothenate after failure of healing during treatment with other members of the vitamin B complex.

REFERENCES

- Field, H., Jr., Parnall, C., Jr., and Robinson, W. D.: N.E.J. Med., 223:307, 1940.
- Garcia, F. T.: Revista Clinica Espanola, 1:231, 1940.
- Kruse, H. D., Sydenstricker, V. P., Sebrell, W. H., and Cleckley, H. M.: Pub. Health Rep., 55:157, 1940.
- Rosenblum, L. A., and Joliffe, N.: J.A.M.A., 117:2245, 1941.
- Vilter, R. W., Bean, W. B., and Spies, T. D.: J. Lab. and Clin. Med., 27:527, 1942.
- Stannus, H. S.: Trans. Roy. Soc. Trop. Med. and Hyg., 5:112, 1912.
- Stannus, H. S.: Trop. Dis. Bull., 33:815, 1936.
- Sebrell, W. H., and Butler, R. E.: Pub. Health Rep., 53:2282, 1938.
- Smith, S. G., and Martin, D. W.: Proc. Soc. Exp. Biol. and Med., 43:660, 1940.
- Machella, T. E.: Am. J. Med. Sc., 203:114, 1942.
- Wintrobe, M. M., Miller, M. H., Follis, R. H., Jr., Stein, H. J., Mushait, C., and Humphreys, S.: J. Nutrit. 24:345, 1942.

Fatty Hepatomegaly with Pancreatic Fibrosis Controlled By Lipocaine

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IN 1924, Fisher (1) and Allan, Bowic, Macleod and Robinson (2) reported that depancreatized dogs died with symptoms of liver failure usually within three

or four months even though adequately treated with insulin and diet. At autopsy the chief abnormality found was a marked enlargement and fatty infiltration in the liver. Macleod and his associates also demonstrated that the fatty infiltration in the liver could be

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prevented by the addition of raw pancreas to the diet. In 1930 and 1931, Hershey (3) and Hershey and Soskin (4) showed that similar preventive effect could be secured by the addition of 10 grams of lecithin to the daily diet of the depancreatized insulin treated animal. In 1932 and 1933, Best and his associates (5) demonstrated that choline was the active constituent of lecithin in this effect. Subsequently, Best found that a number of additional substances exhibited a lipotropic effect, particularly with respect to the type of fatty liver which develops in rats fed on a low-protein and high-fat diet.

In 1936, Dragstedt and his associates (6) demonstrated that the beneficial effect of pancreas feeding in preventing the development of fatty infiltration in the liver in depancreatized dogs could not be accounted for on the basis of its content of pancreatic enzymes or of lecithin or choline. Liver and brain with a higher content of choline and lecithin than was present in pancreas were found to have no preventive effect in depancreatized dogs. The active principle was believed to represent a second internal secretion of the pancreas and was called by Dragstedt lipocaic, as indicating that it was in some way concerned with the metabolism and utilization of fat. Active preparations of lipocaic were secured in fat-free alcohol extracts of pancreas, containing no pancreatic enzymes and little or no choline. The syndrome of lipocaic deficiency, as described by Dragstedt, in the depancreatized dog is characterized as follows: progressive decrease in appetite and activity, progressive loss in weight and subcutaneous fat, progressive decrease in glucose excretion and insulin requirement, gradual impairment in liver function, as evidenced by abnormal retention of bromsulphalein, decrease in the concentration of the total blood lipids and appearance of hepatomegaly and fatty infiltration of the liver as revealed by exploratory laparotomy and biopsy. These abnormalities in the depancreatized dogs are returned to normal by the oral administration of lipocaic. Several reports have appeared in the literature indicating that the syndrome of lipocaic deficiency may occur in man as well as in the experimental animal and that man also responds to the administration of lipocaic. Snell and Comfort (7) described a case of hepatic dysfunction and enlargement as presumably secondary to pancreatic lithiasis and atrophy with improvement during the first twelve days of lipocaic therapy. Grayzel and Radwin (8) treated three young diabetics with marked hepatomegaly with lipocaic and obtained prompt reduction in the size of the enlarged liver with return of the hepatomegaly when lipocaic was discontinued and further improvement when lipocaic was subsequently resumed. Rosenberg (9) described a remarkable case of fatty metamorphosis of the liver proved by laparotomy and biopsy, which was entirely restored to normal by the administration of lipocaic and checked by a second laparotomy with biopsy of the liver.

For the past year and one-half, we have had under observation and study a patient who exhibits many of the signs and symptoms of lipocaic deficiency. During this period, she has been hospitalized five times. The

administration of lipocaic, furnished by Dr. Dragstedt's laboratory, has produced a striking decrease in the size of the enlarged liver, stabilized the fat concentration of the blood and improved the liver function. Accompanying these changes were a definite gain in weight, restoration of appetite and a sense of well-being. The withdrawal of lipocaic has repeatedly caused the re-establishment of the syndrome within a remarkably short period of time.

CASE HISTORY

May 15, 1941, E.B., a white female, was admitted to the Presbyterian Hospital with the following complaints: dull pain in the upper right and left quadrants of the abdomen, nausea, vomiting, night sweats, loss of weight, thirst, frequency and nocturia, cough nervousness insomnia and loss of appetite. She had enjoyed excellent health until three years ago at which time she first noticed the development of unusual fatigue, which has become progressively worse to the present. Pain in the upper abdomen became acute a week before admission. It was not relieved by alkalies or food and was associated with nausea and retching. During the past six months she has lost 29 pounds in weight, during which period she has taken relatively large amounts of paraldehyde for the relief of insomnia and pain. The details of the physical examination and laboratory studies are omitted except for certain relevant items.

The patient was markedly emaciated, weight seventy-five pounds, blood pressure 98/70. The liver was palpable nine centimeters below the costal margin in the mid-clavicular line and was tender on pressure. Cholecystogram revealed a non-functioning gall bladder. The basal metabolic rate was +22. The prothrombin concentration, as determined by Quick's method was 122 per cent. On May 26, 1941, an exploratory laparotomy was performed by Dr. Edwin Miller. The right lobe of the liver was found to be very much enlarged, extending almost to the level of the umbilicus. The surface was pinkish-yellow in color and somewhat mottled. The margins were very round. The left lobe was likewise enlarged. The gall bladder and bile ducts were not abnormal. The pancreas was about the size of an English walnut, three to four centimeters in diameter and was very hard throughout its entire extent. It had the hardness of a carcinoma, but because of diffuse involvement it was concluded that the change in consistency was due to fibrosis. The appendix was removed and the abdomen closed. Recovery from the operation was uneventful and on June 3rd, examination of the blood revealed a cholesterol content of 280 mgm. per cent. Total protein 6.57 grams, albumin 2.91 grams, globulin 3.66 grams, A/G ratio 0.80, amylase 129 units, lipase 0.68 c.c. N/20 NoOH total lipids 1216 mgs, lipid phosphorus 17.0 mgms, cholesterol esters 249 mgms. per cent. The Hanger test of liver function was positive for liver impairment.

From May 29th, until August 15th, four grams of lipocaic, together with a high carbohydrate high-vitamin diet, was administered daily. By June 10th, the patient had gained eleven pounds in weight the liver

was no longer palpable and she was discharged from the hospital. At this time the diagnosis was chronic pancreatitis with cirrhosis and fatty infiltration of the liver. After leaving the hospital she continued to gain weight, reaching 104 pounds in the middle of August. From this date on, however, she experienced a steady decrease in weight and loss of appetite. Irregular eating habits and persistent insomnia developed. A good deal of alcohol, nembutal and seconal were taken and the diet was insufficient in amount and quality. Loss in weight, nervousness, tremor and insomnia became progressively worse until the patient returned to the hospital on June 16, 1942, a little over a year since the previous discharge. At this time she weighed 83 pounds and the liver margin was again palpable 9 centimeters below the costal margin and was tender to pressure. Examination of the blood revealed total lipids 784 mgm. cholesterol 244 mgm. prothrombin 148 per cent. Lipocaic therapy was again resumed in doses ranging from 2 to 10 grams per day. A remarkable recession in the hepatomegaly occurred so that in four days the liver was no longer palpable. On December 21, 1942 her weight returned to 97 pounds, the liver was not palpable, the total blood lipids were 1292 mgs., and total cholesterol 264 mgs. per cent. Lipocaic was then stopped for two months without recurrence of hepatomegaly. On February 20, 1943 the total blood lipids were 1140 mgs., total cholesterol 77.5 mgs. and free cholesterol 50 mgs. per cent. Lipocaic was administered daily until May 15, 1943 and during this

period the blood lipids remained within the normal range (1093 mgs. on 4-17 and 1097 on 5-15), hepatomegaly did not recur, and the general health was better than for many years.

COMMENT

The appearance of pronounced fatty infiltration of the liver in this patient together with evidence of extensive fibrosis of the pancreas as revealed at the exploratory operation suggests an inter relationship between the two phenomena. This is further substantiated by the large amount of experimental data indicating that removal of the pancreas causes a similar hepatomegaly and fatty infiltration in spite of the administration of insulin. Exacerbation of the hepatomegaly due to the ingestion of large amounts of alcohol which occurred several times in this patient is interesting in view of Connor's (10) observations that fatty infiltration of the liver represents an early stage in the development of cirrhosis. The complete recession of the hepatomegaly and striking clinical improvement produced by the administration of lipocaic presents good evidence that a deficiency of this secretion due no doubt to the fibrosis of the pancreas was the underlying factor in the cause of the disease. While biopsy of the liver in this case after recovery could not be obtained, the positive findings of Rosenberg (9), the experimental data, and above all the remarkable clinical improvement of the patient, suggest that the liver has returned to a normal state.

REFERENCES

1. Fisher, N. F.: Amer. Jour. Physiol., 67:634, 1924.
2. Allan, F. N., Bowie, J. J., Macleod, J. J. R., and Robinson, W. L.: Brit. J. Exper. Path., 5:75, 1924.
3. Hershey, J. M.: Amer. Jour. Physiol., 93:657, 1930.
4. Hershey, J. M., and Soskin, S.: Amer. Jour. Physiol., 98:74, 1931.
5. Best, C. H., Ferguson, H. C., and Hershey, J. M.: J. Physiol., 79:94, 1933.
6. Dragstedt, L. R., Prohaska, J. Van, and Harms, H. P.: Am. Jour. Physiol., 117:175, 1936.
7. Snell, A. M., and Comfort, W. M.: Amer. Jour. Digest. Dis. and Nutrit., 4:215, 1937.
8. Grayzel, H. G., and Radwin, L. S.: Amer. Jour. Dis. Child., 56:22, 1938.
9. Rosenberg, D. H.: Amer. Jour. Digest. Dis., 5:607, 1938.
10. Connor, C. L.: Amer. Jour. Path., 14:347, 1938.

Book Reviews

Photomicrography: Theory and Practice. By C. P. Stillaber. Pp. 773, (\$10.00). New York, John Wiley and Sons, 1944.

Because of the tremendous amount of data and valuable information contained in it, this book will most certainly receive a welcome reception by all interested in either microscopy or photography. It is written in a clear style and the technical terms used are explained in either a glossary or the introductory chapter. The inclusion of 140 illustrations further helps in clarifying the context matter.

Unfortunately the author does not include certain aspects of photomicrography which in recent years

have been found to be extremely useful. Color photomicrography, the use of infrared and ultraviolet light, and polarized light are subjects not discussed. The reason advanced for the omission of these important subjects is that their inclusion would have made the book too bulky and expensive. However, this problem could have been solved by condensing certain other sections, such as those on different types of cameras and on optical constants.

This book may be highly recommended to all interested in microscopy, whether professional worker or novice. It should prove of especial interest to the laboratory technician and advanced microscopy student.

Malaria: Its Diagnosis, Treatment, and Prophylaxis.

By W. N. Bispham. Pp. 197. (\$3.50). Baltimore, Williams and Wilkins, 1944.

This book should prove useful to medical students and others interested in problems of public health and parasitology. Malaria is a disease about which the public and the practitioner in this country should be more fully informed since it will no doubt become one of our own major problems. Returning members of our armed forces will certainly bring many tropical and sub-tropical diseases with them and malaria will probably be in preponderance. In addition, we must remember that we have our own malarial areas in these United States which still remain to be cleared. Colonel Bispham presents a complete description of the disease, its clinical aspects, pathology, and treatment, which will be found very readable. This volume is recommended as required reading by all medical men who expect to encounter malarial disease in their present or future practice.

Venenos Sociales. By Pablo Osvaldo Wolff. Pp. 81, Buenos Aires, 1943.

This book contains most of the material used by the author for a series of lectures in 1940. The subject of "Social Poisons" is considered by Doctor Wolff in an interesting manner tho we believe that not all readers are likely to agree with him. From a discussion of the general principles of poisons he proceeds to a consideration of the pharmacologic action of particular drugs which may be considered as poisons under certain conditions. The particular drugs with which most of the book deals are alcohol, opium, cocaine, marihuana and the barbiturates. Doctor Wolff of course recognizes that most substances, even commonly used foods such as milk and eggs, may become "poisons" under certain conditions. However, the drugs he has chosen certainly require attention from the medical profession because of their use as "social" poisons. Alcoholism and opium addiction are examples he stresses. He makes out a case for the relationship between intoxication and criminality. His warning about the use of barbiturates certainly is timely.

My Second Life: An Autobiography. By T. H. Shastid. Pp. 1174. (\$10.00). Ann Arbor, Michigan, George Wahr, 1944.

In ordinary times this biography by a country doctor would probably find numerous appreciative readers. Written partly in the "I remember when" style and partly in the "Once upon a time" style, this volume really is amusing and interesting. It is full of anecdotes, mainly about local celebrities little known outside the confines of their county, but stories about Lincoln, John Hay and others are included too. We do not object to the book at all: we owe the doctor a debt for contributing much to the history of the general practice in by-gone days. But we do question the wisdom of publishing this profusely illustrated

hook of nearly 1200 pages in times like these. Surely, with the paper shortage so acute and the manpower problem unsettled, the paper and labor might well have been devoted to better purposes. But stop! What is this pile of mail before me? Ads, Ads, Ads, Quack, Quackery! Write on and publish more good Doctor Shastid! When commercial houses will cease filling my waste-paper basket with printed blurbs on paper much needed elsewhere, then shall I take you to task again!

Medical Uses of Soap—A Symposium. Edit. by Morris Fishbein. Pp. 182 (\$3.00). Philadelphia, J. B. Lippincott Co., 1945.

The authors contributing to this symposium are all authorities in their particular fields and each has contributed to the medical or chemical literature on his subject. The chemistry of soap and the technical details of its manufacture are adequately covered for the book's purpose by two soap chemists. A brief description of the new detergents is given; with the increasing use of detergents in home and industry this portion might well have been made longer. The chapters of interest to the physician are those dealing with the usual effects of soap on normal skin and hair and the skin reactions to soap which are sometimes seen in patients with peculiar sensitivities. The uses of soap in medicine are discussed briefly. The soap enema is discussed very briefly indeed—to be exact, in just three sentences. A matter of such importance should have been covered in more detail. Most of the chapters have selected bibliography lists appended.

Patología Digestiva Del Niño: Las Diarreas Los Teteros. By Guillermo A. Fraser. Pp. 226, Bogota, Colombia, Editorial Minerva S. A., 1941.

Doctor Fraser's book discusses in fair detail the digestive diseases of the new-born and considers various problems associated with the artificial feeding of infants. In the words of the author, the book is designed "not for the pediatricians in large cities who have at hand the best of diagnostic methods, but for the general practitioner whose facilities for diagnosis are limited to the barest essentials." For this reason this book is found to lay more stress on the clinical pictures than on laboratory procedures for diagnosis.

According to the author, digestive disorders in infants may be classified as falling into one of the following four categories: disorders resulting from faulty enzyme action (on casein and fats in particular), diseases due to obstruction, infections of the digestive tract, and diseases resulting in disturbances of the acid-base balance. The treatment and diagnosis of the large variety of pathologic conditions are given from the viewpoint of the practicing pediatrician. The information presented is based on the experience gained from a study of 2,500 cases. A brief discussion of the anatomy and physiology of the digestive system in the infant is included.

Bronchial Asthma. By Leon Unger. With an introduction by Morris Fishbein. Pp. 724 (\$9.00), Springfield, Illinois, C. C. Thomas, 1945.

This is the most ambitious treatise ever published on bronchial asthma. It is written by an author who is an authority in this field and who succeeded admirably in presenting the rather complex subject in a clear, informative and practical way. Every physician who is called upon to treat asthmatics will do well to read this volume.

This book begins with a fascinating historical introduction adorned by pictures of the leading ancient and modern authors who furthered the knowledge of allergy and asthma. Five chapters are devoted to etiology, including the important predisposing, contributory, and exciting factors. After pathology and symptomatology are exhaustively discussed, diagnosis including skin testing is presented in lucid style. Three chapters enable the reader to evaluate the specific and non-specific treatment, which latter runs the whole gamut from drug therapy to psychic and operative procedures. A very timely discussion on the military aspects of bronchial asthma and other allergic diseases closes the first part of the book. The second part, the laboratory section, will be welcomed by physicians and technicians alike who are called upon to make their own extracts. A very informative appendix is included and is particularly helpful to the patient giving instructions as to how to avoid undue inhalation of dusts, how and when to perform physical exercises, and how to prepare elimination diets. The book workmanship from the technical angle is excellent. The monograph is highly recommended to the practitioner and specialist alike.

Anales del Dispensario Publico Nacional. Edit. by C. B. Udaondo. Vol. 6, Pp. 843, Buenos Aires, Aniceto Lopez, 1943.

The full title of this volume is Annals of the National Public Dispensary for Diseases of the Digestive Tract. It contains 33 articles by a number of eminent South American gastroenterologists. The length of the various papers ranges from ten pages to 100 pages, depending on the relative importance or interest of the subject matter. Physiological, pharmacological, pathological and surgical aspects of various digestive tract conditions are discussed and illustrated with diagrams and roentgenograms. Included among the papers are

such subjects as pruritis ani, chronic ileitis, ulcerative colitis, pathogenesis of pancreatitis, urogastrone and the treatment of ulcers, relation between angina pectoris and digestive tract affections, surgical treatment of cancer of the colon, benign gastric tumors, duodenopancreatectomy in cancer, the irritable colon, pharmacological principles in alkali-therapy, and peptic ulcer of the esophagus. Much more of interest is also included. It is unfortunate that English summaries of the papers were not appended so that these studies could be read more widely.

Outline of the Amino Acids and Proteins. Edit. by Melville Sahyun. Pp. 251. (\$4.00). New York, Reinhold Publishing Corp., 1944.

Twelve chapters written by the editor and a staff of thirteen collaborators comprise this book. Following a 25 page discourse by Sahyun on the history of the discovery of the various amino acids come chapters on the occurrence, amino acid content and properties of proteins (by C. L. A. Schmidt), protein structure (by Henry Bull), synthesis of amino acids (by H. E. Carter and I. R. Hooper) and methods of analysis (by David M. Greenberg). These, together with an account of hydrolysis of proteins by Sahyun, constitute the chemical portion of the book. The more physiological portion of the book, concerned with the metabolism and role of amino acids in nutrition and the relation of amino acids to processes of immunity and detoxication are by Armand Quick, Michael Heidelberger, W. M. Cahill, Arthur H. Smith, Madelyn Womack and C. F. Kade. The entire book is well written and is recommended for its clarity in exposition. Each chapter is followed by a fairly extensive bibliography. Two novel features of the book are worth noting. Heading each chapter is a portrait of an individual who is known for his scientific contributions to the field of protein chemistry or metabolism. Among those so honored are Emil Erlenmeyer, Justus Liebig, Ernest Schulze, Albert Kossel, Emil Fischer and L. B. Mendel. The second feature is an appendix listing the United States patents issued on amino acids and related organic compounds. To those interested in the practical or commercial side of amino acid chemistry this list should prove useful. While only 13 patents are listed as being issued prior to 1930, during the single year 1940 there were issued 19. This may serve as an index of the interest taken in amino acids by the applied physiologist and chemist.

Oral Therapy for Pruritus Ani.

By

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PRURITUS ANI has always been a difficult and baffling problem to the proctologist. It is characterized by a long history of itching of the perianal skin, which becomes reddened, fissured and sometimes moist and macerated. It is notable for its chronicity and resistance to treatment. No one form of therapy has been effective, as is evidenced by the lengthy list of measures employed.

It is therefore, most interesting to come upon a method of treatment, mainly oral, that gives prompt symptomatic relief and which produces clearly visible results in the skin. It is aimed at the most likely site of origin of the condition,—the nervous system.

There are, of course, a few cases of pruritus ani, and very few indeed, which have some obvious cause that is local or general. Fistulae, infected crypts, fissures or polpi, in rare instances, have caused marked itching. Correction of food allergies, liver conditions, eczemas or ringworms, has occasionally helped. It is not too uncommon to find that the cause of the trouble is an irritating, caustic soap used on the skin and bedclothes. Pin worms and even multivitamin capsules can sometimes cause an itch. However, one can almost say, that in ninety-five percent of the cases seen by the proctologist, no observable lesion or disease can be demonstrated.

The one definite and positive finding that stood out in all the cases that I have carefully studied for the past ten years or more, was this: every one of them was highly nervous. The patient might have denied this at first, but sooner or later admitted it and then went into details. Invariably there had been a period of strain about the time of the onset of this distressing condition. There may have been financial difficulties; failure to obtain promotion, or new and overwhelming responsibilities. Others were simply too keen, and were so highly intelligent and ambitious, that they were driving themselves at too fast a pace. There was definitely an emotional disturbance, and it was having its most marked effect upon the digestive tract. Those patients ate hurriedly, complained of gas, were rarely constipated and continually washed the itching area with soap and water. This gave temporary relief but did more harm than good.

In every case, a careful sigmoidoscopic examination was done, along with stool smears and urinalysis. In many instances, barium enema or a complete gastrointestinal x-ray series were ordered. Blood lipase determinations, blood counts, basal metabolism rates, and other tests were made, but were gradually discarded, as no consistent findings appeared. In the gram stain smear of the stool, *B. Coli* were usually high; often ninety percent, and this was felt to be consistent with some inability to digest carbohydrates.

The treatment I applied for many years, followed the usual lines, except that cutting of the perianal nerves or local injection of alcohol were never done. These were only temporary and dangerous measures; often resulting in slough and incontinence. Oil soluble anesthetics, most helpful in all operative procedures, were useless for Pruritus Ani. They gave only a few weeks of relief, and patients always refused to have the injection repeated. Intravenous solutions of Methenamine were used with slight effect. Local chemicals, phenol, silver, mercury and tar compounds did no good. X-ray therapy gave some relief but apparently could not be repeated with safety.

Finally, the following routine was adopted, and a number of cases slowly improved over the months and years, and a few stayed well. Locally soap was avoided for periods of weeks, and cleansing of the perianal area was done only by means of a bland oil. Laundry was to be done only with the finer soaps, which meant the bedclothes and underwear had to be done at home. Medication given by mouth, helped the problem considerably but very slowly. This was a capsule containing Takadiastase, gr. 5; Novatropin, gr. 1/24 and Phenobarbital, gr. 1/3. The Takadiastase aided in digestion of starches, which is the largest factor in nervous indigestion,—according to Alvarez. The Novatropin is an antispasmodic and the Phenobarbital is, of course, a mild nerve sedative. The sedative action, however, did not seem to go far enough, and larger doses produced unpleasant effects. A certain amount of psychotherapy and advice on basic problems was definitely indicated, but was extremely difficult to apply in these busy times.

The new factor that was finally able to change the entire picture was Sodium Dilantin—(Diphenylhydantoin). This drug, an anticonvulsant with little hypnotic effect, seemed to embody the desired principles, and experience has born this out. It is added to the above formula, and one and a half grains were given before each meal, and upon retiring. This gives a total of six grains a day, and it can gradually be reduced as improvement is noted. Reports of the use of Sodium Dilantin for epilepsy, state that even a daily total of nine grains is safe; this quantity would never be necessary for the treatment of Pruritus Ani. Toxic symptoms are dizziness, muscular incoordination, gastric disturbances, swelling of the gums, excessive activity or loss of weight. *(Lennox). Only one case in this series showed slight muscular difficulty, and a decrease in dosage eliminated the problem. Another developed a barbital rash; the phenobarbital was removed from the prescription, and the treatment continued satisfactorily.

The effect of the addition of Sodium Dilantin, in

the oral medication was rather striking. Even long standing cases obtained marked symptomatic relief within a few days, and within a week, reported that itching was only felt after a bowel evacuation. At this time, the skin was found to be undergoing a definite change. Moisture had disappeared, and the deep redness had decreased in intensity as well as in area. The shallow fissures between skin folds were less evident, and the skin itself appeared more elastic.

made, in order to accurately analyze the changes that occur. It would seem to me that the nervous state of the patient originally caused some excessive or abnormal secretion to take place in the mucosa of the lower bowel. Leakage of this material, even though imperceptible at times, must have been occurring at the anal orifice. Reduction of the secretion produces marked clinical improvement. Chemical studies of the process should produce most interesting findings.

Table I

Patient	Sex	Dura-	Area	Moisture	Skin	Other	Marked Symptomatic Relief Within:	Normal Skin Appearance	Recurrences
V. O.	M.	2 yrs.	8 in. present	several	none	ext. hem.	1 wk.	8 wks. —	none in 5 mos.
M. L.	F.	3 yrs.	6 " present	several	ext. hem.	anal fissure	1 wk.	4 " —	once, for 1 wk. (alcohol)
E. H.	F.	2 "	6 " present	bleeding	anal fissure	4 das.	4 " —	none in 3 mos.	
C. L.	M.	7 "	8 " present	shallow	dorsal ulcer	1 wk.	5 " —	none in 5 mos.	
S. L.	M.	4 "	2 " none	few	none	ext. hem.	1 wk.	3 " —	none in 4 mos.
F. S.	M.	20 "	8 " marked	several	none	int. hem.	2 das.	3 " —	none in 3 mos.
J. R.	M.	5 "	2 " none	few	none	int. hem.	3 das.	2 " —	none in 2 mos.
E. G.	F.	10 "	10 " none	several	none	ext. hem.	1 wk.	3 " —	once, for 2 das. (alcohol)
J. K.	F.	4 "	3 " none	several	ext. hem.	int. hem.	2 das.	2 " —	none in 3 mos.
S. M.	F.	7 "	12 " marked	several	several	ext. hem.	1 wk.	10 " —	trace remains
J. C.	M.	1 "	12 " marked	several	several	int. hem.	1 wk.	4 " —	once, for 2 das. (alcohol)
J. K.	M.	10 "	7 " moderate	several	several	int. hem.	1 wk.	2 " —	none in 3 mos.
R. A.	E.	10 "	12 " marked	several	several	pruritus vulvae	5 wks.	8 " —	trace in 3 mos.
M. S.	F.	3 "	2 " none	few	none	ext. hem.	10 das.	4 " —	none in 3 mos.
H. S.	M.	2 "	2 " none	few	none	int. hem.	1 wk.	4 " —	none in 3 mos.
W. C.	M.	2 "	3 " present	several	few crypts	ext. hem.	2 wks.	5 " —	none in 4 mos.
F. K.	F.	5 "	4 " present	several	several	int. hem.	6 das. trace	remains	at 8 weeks
J. P.	M.	8 "	2 " none	few	none	ext. hem.	1 wk.	4 " —	none
R. C.	F.	20 "	5 " present	several	none	int. hem.	1 wk. trace	remains	at 8 weeks
K. W.	F.	10 "	3 " present	few	several	ext. hem.	4 das.	3 " —	none
D. S.	F.	5 "	3 " present	several	several	int. hem.	1 wk.	4 " —	slight at 8 wks. alcohol
J. McK.	M.	30 "	10 " present	several	several	int. hem.	1 wk. 25%	remains	still washing area
M. R.	F.	5 "	2 " none	few	several	ext. hem.	3 wks. trace	remains	none in 3 mos.
M. R.	F.	2 "	2 " none	few	several	int. hem.	4 das.	2 " —	none in 2 mos.
B. F.	F.	10 "	3 " present	several	several	ext. hem.	2 wks.	4 " —	none in 3 mos.
M. B.	M.	4 "	3 " present	several	several	int. and ext. hem.	3 wks.	5 " —	none in 5 wks.
D. M.	F.	1 "	2 " none	few	several	int. hem.	1 wk.	4 " —	none in 4 mos.
M. O'N.	F.	1 "	2 " none	few	several	ext. hem.	1 wk.	3 " —	nervous state
O. C.	M.	3 "	8 " marked	several	several	ext. hem.	3 wks. trace	remains	not taking med. reg.
L. T.	F.	1 "	6 " marked	several	several	ext. hem.	1 wk. trace	remains	bleeding gums (med. stopped)
J. G.	M.	10 "	3 " slight	several	several	ext. hem.	2 wks.	2 " —	none
R. McM.	F.	4 "	4 " marked	several	several	ext. hem.	1 wk.	4 " —	none
A. R.	F.	3 "	3 " none	several	several	ext. hem.	1 wk.	4 " —	previous x-ray therapy
P. T.	M.	20 "	12 " none	several	x-ray dermatitis	ext. hem.	1 wk.	5 " —	none as yet
M. G.	M.	1 "	2 " none	few	several	ext. hem.	1 wk.	3 " —	none
L. V.	F.	1 "	2 " none	several	several	ext. hem.	1 wk.	3 " —	none
F. S.	F.	5 "	3 " none	few	several	ext. hem.	2 wks.	3 " —	none
L. M.	M.	2 "	2 " none	few	several	ext. hem.	1 wk.	3 " —	none
S. W.	M.	3 "	3 " present	few	several	ext. hem.	1 wk.	5 " —	none
S. V.	F.	3 "	3 " present	several	several	ext. hem.	1 wk.	4 " —	none
M. S.	F.	4 "	4 " none	few	several	ext. hem.	1 wk.	5 " —	none
M. R.	F.	1 "	1 " none	few	several	ext. hem.	1 wk.	4 " —	none

Within another week or two these fissures had completely disappeared. It was interesting to note that these fissures now responded very quickly to an application of silver nitrate solution—25%. Without oral medication, the response had been practically nil. An occasional saline enema during the first week helped speed up the process.

More study of this whole reaction will have to be

Salivary, gastric and intestinal secretions may also be involved.

In this series of forty-two cases, one showed no improvement; and another has recovered very slowly. Almost all the others responded in a surprisingly short time. The unsatisfactory response was that of an extremely nervous young man, whose problems, both marital and financial, were so acute that he could

neither eat, sleep or take medication with any regularity. He was advised to seek first aid from the legal profession, and then to report for medical treatment; when some continuity of medication could be assured. The sluggish response was that of a woman going through the menopause. Before the addition of Sodium Dilantin, she was growing progressively worse, and the pruritus was rapidly spreading from the anal region to the vulva, and finally to the suprapubic area. Moisture, maceration and fissuring were severe. It was impossible for her to obtain more than a few hours of sleep without interruption, and all measures seemed ineffectual. Within a week after the addition of Dilantin, she was able to sleep through the whole night. Moisture disappeared at the end of three weeks, but at the end of five weeks, there were a few isolated areas that itched on days of greatest exertion. At the end of eight weeks, the area was practically normal in color and general appearance, and no itch was present.

In this case, and in the case of a few others that showed delay in recovery, certain facts were observed regarding control of the treatment. Mineral oil is contraindicated in the individuals who are constipated; a slight leakage is present and this interferes with the healing of the skin margins. Alcoholic excess definitely retards recovery, and caused a temporary return of the pruritic conditions in two cases. Condiments and fried foods may possibly have some delaying effect, but beyond this, diets are not restricted to any marked degree.

The problem of recurrence must be considered. The earliest cases in this series, date back five months. Treatment was used for four to six weeks and then was stopped entirely. Symptoms did not return, and the skin has retained a normal appearance at the time of each "check up". Other cases, more recent, have

also stopped medication, and have had no complaints. Two individuals had a brief return of symptoms—each about forty-eight hours. The routine was begun again and symptoms quickly disappeared.

Definite knowledge regarding recurrence cannot possibly be obtained until a large number of cases have been followed for two years or more. The possibility of return of symptoms has been freely discussed with patients. Their reaction is interesting. They say they have no fear of the condition now that they have available a simple, prompt remedy. It is hoped that this attitude in itself will afford some help to the psychic side of the problem.

SUMMARY

1. 42 Cases of Pruritus Ani were treated, with oral medication and local applications.
2. History of the duration of symptoms varied from 1 to 30 years. Three cases also had Pruritus Vulvae.
3. A formula containing Takadiastase and Sodium Dilantin made an effective combination. Dilantin alone did not control the condition.
4. Soap and water are avoided at first, and local cleansing is done with olive oil. Laundry is to be done only with the finer soaps.
5. Silver Nitrate is accurately applied to the skin fissures as well as those within the anal canal. Judgment must be exercised as to the quantity used and the strength of the solution.
6. Alcohol, mineral oil, condiments and fried foods are omitted entirely.
7. Duration of treatment varies with individual cases. Those who are constipated are slower to recover.
8. A recent review of the literature on the subject of Pruritus Ani has failed to disclose any previous treatment of this type.

BIBLIOGRAPHY

- Young, F., etc.: Surgery 6: 911-915, June '43.
 Turell, R.: N. Y. State J. Med. 42: 1335-40, July 15, 1942.
 Slocumb, L.: Amer. J. Digestive Diseases. Vol. 10-*6, June 1943. pp 227-234.
 Cantor, A.: Amer. J. Digestive Diseases. Vol. 10, No. 7, July 1943. pp 254-261.
 Aldrich, R.: Industrial Medicine, 12-Oct. 1943. pp 654-658.
 Boyd, L. & Bellows, E.: Bulletin N. Y. Med. Colleges—Flower & Fifth Ave. Hospitals, April-June 1944. pp 51-64.
 Cantor, J.: Review of Gastro-enterology. Vol. 10, pp 46-49. Jan. Feb., 1943.
 Drueck, C.: Medical Record—155, pp 487-488.
 Bacon, H.: Anus, Rectum & Sigmoid. Lippincott & Co., 1938, pp 152-179.
 Bodkin, M. L. Diseases of the Rectum, E. B. Treat & Co., 1925, pp 279-285.
 Tanberhouse, L.: Treatment of Intractable Pruritus Ani. U. S. Naval Medical Bull., Jan. 1942, pp 136-139.
 Norman, H.: New International Clinics, Vol. LV, Series 4, 1941.
 Turell, R.: Amer. Journal of Obst. & Gyn., August, 1941, pp 290-291.
 Seletz, R.: Western Journal Surg., Obst. & Gyn., 50:289-292, June, 1942.
 Crigler, R.: Journal of Arkansas Med Society, July, 1942, pp 45-46.
 Marino, Buda, Turell: Arch. Derm. & Syphyl.—'41: 521-526, March, 1940.
 Cantor, A.: Amer. Journal of Surgery, Vol. LIII, pp 121-124, July, 1941.
 Hailey, H.: Southern N. J. 34, pp 191-196, Feb., 1941.
 Granet, H.: New England J. Med., Vol. 223. pp 1015-1020, Dec. 19, 1940.
 Seare, G., etc.: New Eng. J. Med., Vol. 223. pp 274-276, Aug. 22, 1940.
 Alvarez, W. C.: Nervous Indigestion, P. B. Hoeber, Inc. 1930.

Neurofibroma; A Gastroscopic Report

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THE gastroscopic incidence of benign tumors of the stomach, according to Schindler (1), is about one and one-half to two percent. Rigler and Erickson (2) found that, in a series of two hundred thirty-nine roentgenologic examinations which revealed tumors of the stomach or duodenum, eleven percent were benign, and, in a second series of one hundred ninety-four necropsy cases of tumors involving the stomach or duodenum, as high as twenty-five percent were reportedly benign. Lest the opinion become prevalent that they are relatively frequent, it might be added that the incidence actually is quite low. Thirteen instances of benign tumor among three hundred thousand consecutive cases were reported at Jefferson Hospital in Philadelphia (3), and, of that thirteen, only one was a neurofibroma. At the Cleveland Clinic (4), there were seventeen benign tumors of the stomach in two hundred fifty thousand consecutive admissions. Twelve of these tumors were examined histologically, and three of them were neurofibromata. Of the benign gastric tumors, leiomyomata are said to occur most commonly by many authors, including Minnes and Geschickter (5), who found that one-third of the nine hundred thirty-one collected cases of benign gastric tumors were leiomyomata; in that same series 10.9 percent were neurofibromata. In the course of one thousand five hundred gastroscopic examinations at the State University of Iowa Hospital, it has been our privilege to see, or at least recognize, only one neurofibroma.

Neurofibromata are occasionally associated with generalized neurofibromatosis. Sometimes, when they accompany cutaneous neurofibromatosis there is a history of hereditary tendency to the disease, and of low mentality and arthritis deformans. In one case, reported by Grill and Kuznia (6), of a neurofibroma involving the ileum about eighteen centimeters from the ileocecal valve, there was a history that one of the sisters had had intestinal obstruction, and the patient herself had had arthritis deformans involving the left arm and shoulder.

Opinion is about equally divided as to where these tumors arise. Such men as Gray (7), Bailey and Hermann (8), believe that the neurofibromata of the stomach arise from the perineurium or endoneurium,

and, hence, are mesodermal in origin. Others, including Masson (9) and Geschickter (10), trace the tumors to proliferation of nerve sheath cells, or the cells of Schwann, which are ectodermal in origin.

The symptoms of neurofibromata, as with other benign tumors of the stomach, are variable, and are never in any degree characteristic of the disorder. The symptoms are indefinite, and depend on size, location and the presence or absence of associated ulceration of the mucosa. Many patients have ulcer-like distress, and some of them get relief with ulcer management. Hemorrhage is another common complaint, with or without other symptoms, varying from occult blood to frank hematemesis. If the tumor is located at the pylorus it may cause obstruction, and if it is pedunculated the obstruction may be intermittent. The smaller tumors, not associated with ulceration, and located in the body of the stomach, usually are asymptomatic and are discovered only incidentally by the pathologist or surgeon. Three of seven neurolemmas reported by Ransom and Kay (11) were accidentally discovered in association with other gastric diseases.

The neurofibromata occur most commonly on the lesser curvature (12) toward the pyloric end of the stomach. Usually, they grow outward from their subserous location into the peritoneal cavity. Occasionally, they project into the cavity of the stomach. In this latter type, especially, the mucosa overlying the tumor may thin out and ulcerate in its most dependent portion. Usually their growth is relatively slow, and they seldom infiltrate the surrounding tissues. About ten percent of them are thought to undergo malignant change, and those changes usually occur when the stomach tumor is associated with generalized neurofibromatosis. Grossly, the tumors are usually gray, grayish-yellow, or pinkish-gray in color—almost translucent. Ordinarily, the mucous membrane covering the benign tumor is smooth, and the surface of the lesion, as a rule, is not markedly nodular (13). The attachment of the tumor is generally localized.

Diagnosis depends on, first, the roentgenologic examination, and second, the gastroscopic examination. The use of small amounts of barium, not to exceed eight ounces, and the taking of several spot films may enable one to make the diagnosis. Typically, the lesion is a smooth-bordered filling defect. Fluororadiograms may give additional information about certain features of the lesion. However, the only sure way to make the diagnosis is by histologic examination.

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The following is a report of one case of neurofibroma found at the State University of Iowa University Hospitals.

This thirty-four year old, white, female patient was admitted to the Iowa University Hospitals January 21, 1943, and was discharged March 2, 1943. She gave a history of having had transient jaundice eleven years before, lasting one week. There had been no recurrence of the icterus since then. During the

was given a modified Meulengracht diet, tincture of belladonna, phenobarbital, and multiple whole blood transfusions. The blood disappeared from the stools, and, on February 2, 1943, roentgenologic examination revealed "a filling defect in the greater curvature near the pylorus, carcinoma or some other type of tumor must be ruled out." Gastroscopic examination on the following day was as follows:

A stomach tube was introduced and thirty cc of thin, bloody, chyme recovered. A trace of free hydrochloric acid was present, but lactic acid was absent as shown by routine chemical tests. Microscopic examination revealed large numbers of red cells, few vegetable cells, but no Boas-Oppler bacilli.

The patient did not cooperate very well causing considerable difficulty in passing the gastroscope. A spasm of the esophagus was encountered lasting about five minutes. At the end of this time the spasm suddenly relaxed and the instrument slipped into the stomach. The interior of the stomach was very dark making it difficult to orient ourselves. The intensity of the light was increased (to about 20 volts on the rheostat) and then we noticed that the mucosa was extremely pale and dry. Depth I was finally reached and here the angulus was small, contracted normally, but was very pale. At no time did we have enough illumination to see into the antrum. In the 10 o'clock position the lesser curvature was seen. A few small folds were present, and an occasional peristaltic wave



FIGURE 1
Surgical specimen showing tumor mass and ulcerated area.

three years before admission, the patient had had a dull distress in her epigastrium almost constantly. Usually, it radiated through to the back, but occasionally around to the right side. No particular kind of food had been noted to aggravate the pain. The pain was not relieved by bowel movements. The patient had had considerable gas on the stomach at times. Five days prior to admission the patient first noted tarry stools. The following day she had syncope, and vomited reddish, dark blood of an unknown amount. More hematemesis occurred that same night. The patient remained in bed thereafter, and fainted twice on attempting to arise. The stools remained tarry. The patient experienced no further abdominal distress.

Physical examination at the time of admission revealed an exsanguinated, slender, white woman with a tachycardia of one hundred twenty a minute and a blood pressure of 130/50. Abdominal examination was negative. Rectal examination revealed tarry feces on the gloved hand.

Laboratory examination revealed 4.7 grams of hemoglobin (Haden-Hauser), 1,650,000 erythrocytes, 14,400 leukocytes and a blood smear which was normal except for erythrocytes which seemed hypochromic. Complement fixation test for syphilis was negative.

The patient was treated medically as a case of bleeding peptic ulcer and severe secondary anemia. She



FIGURE 2
Low grade magnification showing normal gastric mucosa reflected over the tumor mass with a margin of area of ulceration.

was noted. On rotating to the nine o'clock position a mass arising in the anterior wall was seen. This mass was hard, fixed and looked as if a golf ball was imbedded in the stomach wall. The surface was smooth, waxy in appearance, and a few fine blood vessels were noted. The tumor was situated in the anterior wall between the lesser and greater curvatures just proximal to the angulus. Near the greater curvature blood was flowing from the mass, but the point of bleeding was not found.

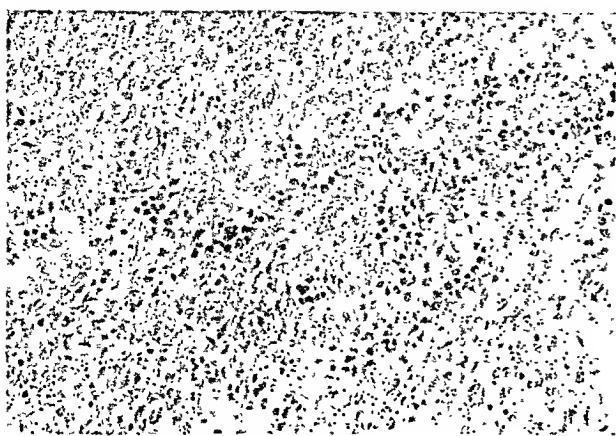


FIGURE 3

High powered magnification of tumor. Scattered lymphocytes indicate low grade inflammatory reaction in tumor.

The instrument was withdrawn into Depth II, and here the anterior wall was pale, had a few fine folds, and several small hemorrhagic areas. Free, dark blood was seen between the rugae along the greater curvature. The posterior wall showed normal folds, very pale mucosa, small hemorrhagic areas and small patches of hard tenacious mucus. Peristalsis in this region was very active. In Depth III the greater curvature was obscured by a large pool of dark, reddish-brown blood. By this time the patient had become extremely restless, necessitating us to terminate the examination.

The gastroscopic impression was—(1) Mass in anterior wall just proximal to the angulus. We were unable to determine whether this was a neurofibroma or lymphoma. (2) Atrophic gastritis. (3) Superficial gastritis.

After a total of eight whole blood transfusions, the

patient was operated on February 12, 1943. An intramural tumor, one inch in diameter, was situated immediately proximal to the pylorus of the stomach (Figure I). Over the surface of the tumor was an ulcerated area three to four millimeters in diameter, looking much like the usual benign ulcer of the stomach. A subtotal gastric resection, removing approximately one third of the stomach, was done. The gastrointestinal tract was re-established by a classical type of Polya anastomosis. Histologically (Figures II and III), the tumor was a "highly cellular neurofibroma." The patient had an essentially normal postoperative course, and was discharged March 2, 1943.

The patient returned for a check-up examination in May, 1943. Roentgenologic examination at that time revealed "pyloric resection, showing a well functioning anastomosis." The gastroscopic examination at that time showed a normal postoperative stomach. Through a recent communication, it was found that the patient was working full time and had no complaints.

SUMMARY

At the time of the gastroscopic examination, the patient had a severe secondary anemia causing an extreme pallor of the gastric mucosa. This extreme pallor was responsible for both the poor visualization and the difficulty encountered in differentiating between a malignant and benign lesion. The ulcerated area was not seen through the gastroscope as it was situated on the distal part of the mass below the greatest diameter of the tumor. Since it is our policy to have all suspicious lesions removed, this was carried out. It is interesting to speculate on the possibility that if we had examined this woman after she had had the transfusions, would the more normal color of the mucosa have enabled us to differentiate between a benign and malignant lesion?

REFERENCES

1. Schindler, R.: The Endoscopic Study of Gastric Pathology. 12:232-233, 1937.
2. Rigler, L. G., and Erickson, L. G.: Benign Tumors of the Stomach; Observations on Their Incidence and Malignant Degeneration. Radiology, 26:6-15, 1936.
3. Shallow, T. A., and Lemmon, W. T.: Benign Tumors of the Stomach. J. International College Surgeons. 3:312-317, 1940.
4. Root, J. C.: Benign Gastric Tumor; Case Report of Neurofibroma. Cleveland Clinic Quarterly. 9:45-53, 1942.
5. Minnes, J. E., and Geschickter, C. R.: Benign Tumors of the Stomach. American J. Cancer. 28:136-149, 1936.
6. Grill, J., and Kuzma, J.: Recklinghausen's Disease with Unusual Symptoms From Intestinal Neurofibroma. Archives of Pathology. 34:902, 1942.
7. Gray, S. H.: Histogenesis of Von Recklinghausen's Disease. Archives Neurology and Psychiatry. 22:91-98, 1929.
8. Bailey, P., and Hermann, J. D.: Role of Cells of Schwann in Formation of Tumors of Peripheral Nerves. American J. Pathology. 14:1-38, 1938.
9. Masson, P.: Experimental and Spontaneous Schwannomas (peripheral gliomas). American J. Pathology. 8:367-388; 389-416, 1932.
10. Geschickter, C. F.: Tumors of Peripheral Nerves. American J. Cancer. 25:377-410, 1935.
11. Ransom, H. K., and Kay, E. B.: Abdominal Neoplasms of Neurogenic Origin. Annals of Surgery. 112:700, 1940.
12. Bockus, H. L.: Gastroenterology. Vol. I, 34:704, 1943.
13. Waltman, W., Gray, H., and Priestley, J.: Carcinoma of the Stomach. 4:67, 1942.

The Diarrhea Problem

By

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A MEDICAL problem is born when difficulty is encountered in the etiologic diagnosis of disease or in the treatment of disease, or both. Tuberculosis, the venereal diseases and the pneumonias presented such problems. That this is true with diarrheal diseases will be evident in the following pages.

Every physician knows that a persistent diarrhea rarely responds to antiseptics, adsorbents, colonic irrigations or opiates. Yet these measures are in wide use at the present time. This is unfortunate, as the first aim of the scientist in his struggle to conquer disease is to seek the cause. Once the cause of the disease is ascertained, therapeutic measures are then considered. With diarrheal diseases this has not been the procedure of attack especially by the general practitioner.

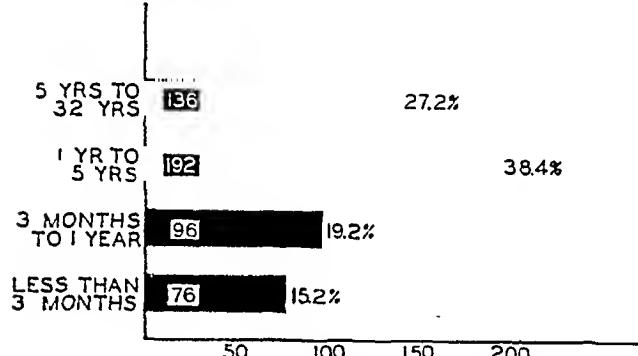


FIG.1: DURATION OF DIARRHEA IN 500 CONSECUTIVE CASES

There are many reasons for this seemingly unscientific approach. First, the problem requires laboratory investigations of a rather specialized type; secondly, the problem requires the cooperation of the patient, which is not always possible on account of his lack of understanding or poor economic state; lastly, the average physician knows that opiate mixtures give immediate relief and, of course, this is the primary wish of the patient. That the relief is only temporary in most cases is common knowledge.

A persistent diarrhea is usually a neglected diarrhea. The patient has already tried all types of home remedies including numerous proprietary preparations, over-the-counter mixtures from his neighborhood pharmacist, and varied types of prescriptions from one or more physicians. By this time the sufferer has starved and drugged himself to almost physical and mental exhaustion. In other words, the etiologic problem has become one of disturbed physiologic and

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metabolic processes which affect every system in the body.

Thus, the diarrhea problem forms a tetrad in which the public, the medical profession, the social service worker and the public health officials have a common goal. The problem concerns the public because diarrheal conditions are responsible for prolonged ill health (1) and enormous economic losses. A review of 500 consecutive cases from office and consultation practice reveals vividly the startling morbidity in diarrheal diseases. Figure 1 shows the duration of the diarrheal condition before the author's examination. Over eighty-four per cent of the patients suffered with diarrhea for more than three months and almost 66% of the patients had diarrhea for periods ranging from one year to thirty-two years.

Diarrheas constitute a most perplexing problem of diagnosis to the physician because the etiologic factors are so numerous. In 1939 the author (2) reported that over one hundred causative agents may be responsible for a diarrheal condition. The search and analysis of so many factors in the diagnosis of a disease involves a well equipped laboratory, and a host of specially trained associates, as well as a great deal of time on the part of the physician. The time element is usually beyond the reach of the busy medical practitioner. In addition, the management and treatment of the diarrhea is so complex that the patient finds it difficult to understand and cooperate with it. For example, the patient fails to realize the importance of sufficient physical and mental rest, the adherence to a non-irritating diet, regular hours of eating, the avoidance of exposure to upper respiratory infections, the importance of eliminating all possible foci of infection and the necessity for continued medical supervision. In other words, the majority of

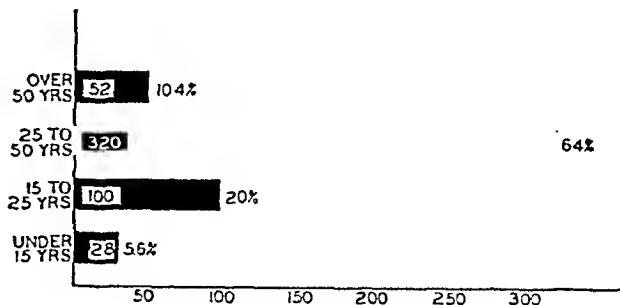


FIG.2: AGE DISTRIBUTION IN 500 CONSECUTIVE DIARRHEA CASES

patients tend to seek a "short-cut" in the treatment.

The importance of the problem to society from both the social and economic aspects is revealed in Figure 2. It shows the age distribution of 500 consecutive cases.

Three hundred and twenty patients, or 64%, were stricken with diarrhea during their most productive period of life, between the ages of twenty-five and fifty years. It is difficult to appreciate the enormous social ramifications of such an anti-social and embarrassing condition during this active age period. One can only surmise the many problems of education, employment, friendships, marital status, childbirth and family relationships which the diarrheal condition has brought about. Occasionally, patients have attempted or committed suicide because of the chronicity of this condition. It is, therefore, evident that these individuals require in addition, the interest and aid of the trained social service worker if they are to be re-adjusted to society.

The problem is of great importance to the public health authorities because of the frequency and high mortality of diarrheal diseases. When 35,000 people of a population of 65,000 are affected simultaneously with diarrhea, as reported by Ziegler in 1937 (3), the importance of the problem to the public health is self-evident. When approximately ten to twelve million people in the United States (4) are estimated

were more deaths from diarrheal diseases than from meningitis, appendicitis, tuberculosis, peptic ulcer or syphilis. During that same period, 3,715 patients were admitted with diarrheal diseases, 624 of whom died, producing the average high mortality of 16.8%.

Table I shows the mortality of diarrheal disease in the United States. During the fourteen year period from 1927 to 1940, diarrheal diseases caused a total of 377,507 deaths with an average annual mortality of 26,965 persons.

Diarrheal diseases present a medical problem which can be met by the united interest and cooperation of physicians, hospitals, social service organizations and public health authorities (8). These four groups must recognize the following facts in any successful working plan:

1. A diarrhea is an urgent laboratory problem.
2. A diarrhea is a vital nutritional problem.
3. A diarrhea requires a segregated hospital service and a specialized laboratory team in cooperation with a special hospital clinical team.
4. A diarrhea must be checked promptly in order

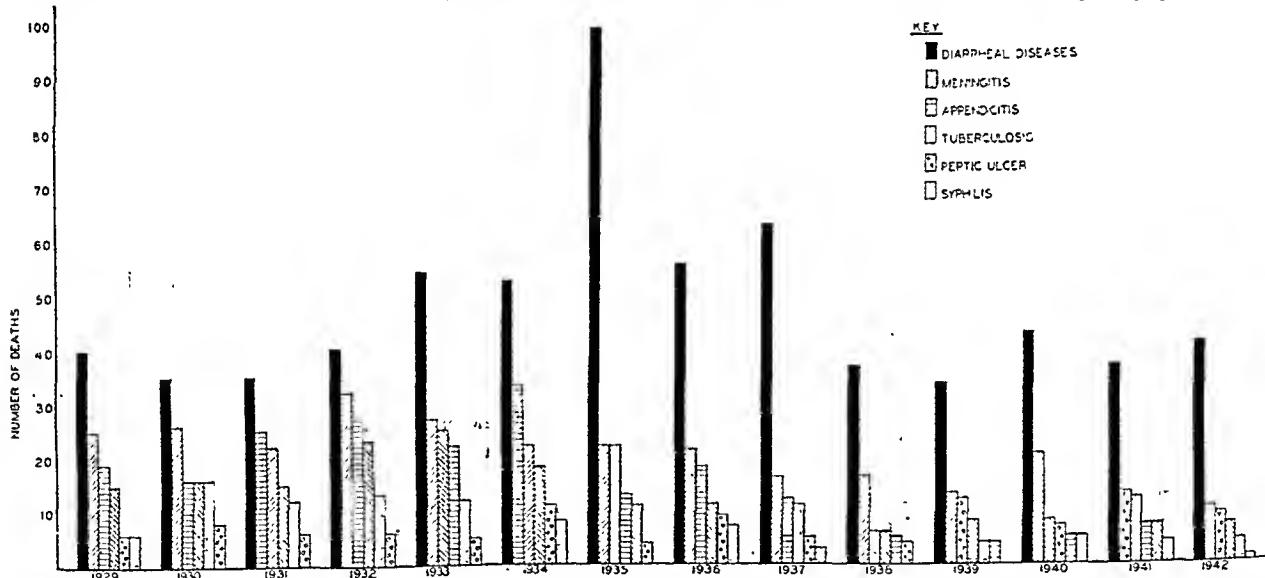


FIG 3 COMPARATIVE MORTALITY OF DIARRHEAL AND OTHER DISEASES IN A GENERAL 600 BED HOSPITAL (NEWBORNS NOT INCLUDED)

to be infected with *E. histolytica*, a well known cause of diarrhea and digestive disorders, the problem becomes nation-wide in scope.

During February 1938, according to a report of the Wisconsin State Board of Health (5), about 4.5% of the population of Milwaukee were suffering with diarrhea. An epidemic of diarrhea in a state hospital was reported by Block and Simon in 1936 (6). Four hundred and seventy-five, from a total of 4,500 inmates, were afflicted. The mortality rate was 14.5%. Hunt (7), in his studies of nine epidemics of diarrhea or dysentery occurring in Pennsylvania, reported 55,000 cases out of a total population of 152,000.

Figure 3 shows the comparative mortality of diarrheal diseases at a general 600 Bed Hospital. In practically every year from 1929 to 1942 inclusive, there

Table I. Mortality of Diarrheal Diseases in the United States

Year	Under 1 Yr.	1-14 Yrs.	Over 14 Yrs.	Total
1927	18,820	9,318	7,201	35,339
1928	18,561	10,599	7,422	36,582
1929	16,558	9,139	6,914	32,611
1930	18,697	10,528	7,697	36,922
1931	15,191	7,673	6,594	29,458
1932	11,644	6,101	5,890	23,635
1933	12,442	7,337	6,500	26,279
1934	14,159	7,229	6,744	28,132
1935	11,446	4,728	5,500	21,724
1936	13,376	6,058	6,044	25,478
1937	12,764	5,105	5,329	23,198
1938	12,572	4,962	5,042	22,576
1939	10,118	3,886	4,632	18,636
1940	9,272	3,459	4,206	16,937
Total	195,620	96,122	85,765	377,507

to avoid serious social, medical and surgical complications.

5. A diarrhea is a menace and potential danger to

the public health.

6. Systematic study of diarrheal diseases will inevitably lead to progress in this field.

REFERENCES

1. Fradkin, W. Z.: Ulcerative Colitis of 28 Years' Duration With Recovery. Amer. J. Dig. Dis. 5:746-749 (Jan.) 1937.
2. Fradkin, W. Z.: The Diarrheal Diseases. N. Y. State J. M. 39:1578-1581 (Aug. 15) 1939.
3. Ziegler, N. R.: Bacteriology of Epidemic Diarrhea. Preliminary Report, Amer. J. Pub. Health. 27:241-246 (March) 1937.
4. Craig, C. F.: The Amebiasis Problem. J. A. M. A. 98: 1615-1620. (May 7) 1932.
5. Wisconsin State Board of Health Reports, Outbreak of Gastroenteritis in Milwaukee and Vicinity. J. A. M. A. 111:716 (Aug. 30) 1938.
6. Block, H.; Simon, A.: Epidemic of Bacillary Dysentery in Elgin State Hospital. Preliminary Report, Am. J. Dig. Dis. & Nutr. 3:305-310 (July) 1936.
7. Hunt, C. J.: Bacillary Dysentery. J. A. M. A. 59:919, 1912.
8. Hardy, A. V.; Watt, J.: The Acute Diarrheal Diseases. J. A. M. A. 124:1173-1179 (April 22) 1944.

General Treatment of Diarrheal Diseases

By

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SUPPORTIVE therapy is vital and often life-saving in the treatment of diarrheal diseases. By its very definition, diarrhea means a rapid flowing through or outpouring of liquid intestinal contents from the bowel. This is accompanied by a tremendous loss of water, salt, proteins, vitamins and all the glandular secretions which empty into the tract as well as the nutrient and fluids ingested orally. It is no exaggeration to state that an individual weighing 150 pounds can lose as much as 20 to 30 pounds within two or three days.

This extreme loss leads to metabolic disturbances which must be recognized early and combatted vigorously before irreversible tissue changes take place. The earliest disturbances are dehydration, hypochloremia and hemoconcentration. The patient presents an emaciated appearance with sunken eyes, dry tongue, loss of skin turgor, low blood pressure, slight fever, oliguria, rise in specific gravity of the blood and urine, rise in blood urea and fall of the blood chlorides. The patient is in a mild state of shock.

Treatment consists of two or three liters of 5% glucose in saline given intravenously daily, until the patient is hydrated and a normal salt level of the blood is obtained. Glucose is added to the saline because these patients have lost their basic caloric supply through the frequent bowel evacuations. They usually refuse fluids orally because they have found that drinking aggravates the diarrhea. Therefore, one must rely on intravenous therapy exclusively.

Simultaneously with the disturbance of water and salt metabolism, there is a great loss of protein from the body because food given by mouth is insufficiently digested or is excreted too rapidly for absorption to take place. This leads to a state of hypoproteinemia.

The patient complains of marked weakness, pallor, puffed eye-lids, pitting of the ankles and coldness of the extremities. Examination reveals generalized edema, marked anemia, rapid pulse, low blood pressure, low blood volume, low serum protein and inversion of the albumin-globulin ratio. One must remember that there also exists an edema of the entire gastro-intestinal mucosa which interferes with the digestion and absorption of food. Consequently, these patients refuse food; and they must not be forced to eat lest they vomit and further aggravate the general metabolic state.

Treatment consists of plasma infusions, blood transfusions, or both. These must be given daily in conjunction with the glucose and saline until the patient is able to take and retain food by mouth. Intravenous amino acid therapy, although theoretically satisfactory, has to date not been practical because of its tendency to increase peristalsis and add to the number of bowel evacuations. When the generalized edema subsides, the patient may be given the high caloric, high protein diet described below. One must not be misled into using digitalis in these cases to reduce the edema and the rapid pulse rate.

After the water, salt, blood and nitrogen balance of the body has been restored to normal levels, the patient suffering with diarrhea must be placed on a special diet. This diet must consist of foods which are easily absorbable and which appear appetizing. It must not stimulate peristalsis, but should rather be constipating. The diet consists of three basic meals per day, with three in-between meals depending upon the appetite of the patient. Each basic meal is rich in proteins, carbohydrates and minerals; moderately low in fat and residue; and high in vitamins. Each of the basic meals is started with six ounces of a tolerable fruit juice, such as orange, tomato or grapefruit.

The patient is not allowed smoking, alcoholic bev-

erages, soups, fried or greasy foods, spices, candy, rich cakes and pastries or fresh milk. Tobacco stimulates peristalsis, interferes with the appetite. It has also been shown that absorbed nicotine will cause vasoconstriction in the terminal arterioles. This limits vascular regeneration and interferes with proper healing. Alcoholic beverages are stimulating and also tend to increase peristalsis. Soups have no, or very little, caloric value. They are gas-producing and take up vital space in the stomach. Chewing gum causes swallowing of mouthfuls of air with the saliva. It leads to distention and a feeling of fullness and introduces the pernicious habit of belching.

This diet must be modified according to the dietary history of the patient and the severity of the attack. If information is obtained that eggs or milk were never part of the patient's daily diet, they are best omitted at the beginning of the treatment. It is best to adjust the diet so that new and strange foods will not greatly alter the patient's likes and dislikes. As the patient improves, each suspicious food is cautiously added and enough time allowed to elapse before the factor of sensitivity is considered. Smooth jellies and jams may be added as the patient improves and as the number of bowel evacuations approach the normal. Chocolate may be allowed after meals, if tolerated. At least eight glasses of water should be consumed daily; more than twice this quantity in very hot weather.

The accompanying diet is ideal for the patient suffering with acute or chronic diarrhea. It is needless to state that the acutely ill will be able to choose only a few of the foods suggested here.

Diarrhea also produces various stages of hypovitaminosis, because of the failure of the gastro-intestinal tract to absorb or digest the rapidly propelled food. The lack of appetite also causes an inadequate intake of food, while the organic changes in the intestine impede absorption. During a chronic infection, it is a common experience to note a disturbed vitamin equilibrium. Therefore, one must be prepared to meet all forms and degrees of vitamin deficiency syndromes, such as mild or severe beri-beri, mild or severe scurvy, mild or severe pellagra, and mild or severe riboflavin deficiency. A description of all these syndromes is out of place in this paper. Suffice it to say that loss of appetite, stomatitis, glossitis and cheilitis developing in the course of a diarrheal disease denote a deficiency in vitamin absorption. Skin lesions, mucosal hemorrhages, paresthesias and headache are also frequently encountered. The distortion of the mucosal pattern of the small bowel as revealed by roentgen studies is a definite manifestation of vitamin deficiency.

Treatment consists of massive doses of thiamine hydrochloride, ascorbic acid, riboflavin and niacinamide, given intramuscularly or intravenously daily in conjunction with other parenteral therapy. This treatment is continued until all signs and symptoms are alleviated. One can readily judge the dosage and frequency of vitamin administration by the condition of the skin, eyes, tongue and buccal mucosa. Crude liver extract should be given intramuscularly, two or

three times weekly for its vitamin B complex content. The accompanying chart will aid the physician in the recognition and treatment of the various vitamin deficiencies. It shows the diagnostic features, normal requirements and range of therapeutic dosage. The amount and mode of administration (oral and parenteral) will, of course, vary with the severity of the diarrhea.

Supportive treatment of a diarrheal disease must include the administration of calcium. The patient suffering with diarrhea is usually poorly supplied with calcium because milk, the chief source of this mineral, is tolerated in small quantities and sometimes not at all. Therefore, it is important to administer calcium gluconate orally or intramuscularly at frequent intervals to insure normal intake. Calcium gluconate, when given intravenously, often relaxes intestinal spasm. The intramuscular route should be used when a more prolonged effect is desired. When calcium gluconate or lactate is given orally, ten to fifteen grains per day should be prescribed in conjunction with adequate doses of thiamin hydrochloride to facilitate the absorption of the calcium through the intestinal mucosa.

When a marked secondary anemia is present, iron may be administered provided it does not aggravate the diarrhea. Iron metabolism is especially necessary for building hemoglobin. It is best given in the form of reduced iron, the patient being instructed to sprinkle it from a salt shaker upon the food at each meal. This should be done very sparingly, lest an increase in the number of bowel evacuations occurs. Capsules of iron, liver and thiamin chloride are available on the market and have proven beneficial. Iron is absorbed chiefly in the duodenum and partially in the stomach and small intestine. It is excreted through the colon, and this fact explains the aggravation of a diarrhea when large quantities of iron are given.

Diarrhea patients require sedatives which depress the central nervous system. Phenobarbital, amytal or the bromides, in small doses, given before meals and again at bed-time, is recommended. Atropine and trantoin are useful in the ambulatory patient who are more susceptible to nervous spasm. The narcotic drugs should be rarely used and then only with extreme caution. The temporary relief produced by narcotic drugs is practically always followed by aggravation of all the symptoms. Opium causes difficulty in expelling stools in spite of an increased desire to defecate. It activates the small bowel, but paralyzes the colon. This stasis may lead to increased ulceration of the colon with unfortunate results. Opiates offer a false state of security for the physician and the danger of bowel perforation for the patient. Hot applications in the form of compresses to the abdomen are more desirable.

Bismuth subcarbonate and kaolin mixtures are occasionally useful during the period of convalescence.

The sulfonamide drugs are potent bacterial antisepsics, somewhat specific in action and best not used until the etiology of the diarrhea is established. It is dangerous, highly unscientific, and most confusing to use these drugs in such cases as neoplastic diarrhea,

gold or cadmium diarrheas, protozoan diarrheas, or any other non-bacterial condition.

When the number of bowel movements decrease to four or five in twenty-four hours, rectal instillations of kaolin and aluminum hydroxide mixtures with mineral oil are advisable. These are retained overnight for their adsorptive, astringent and soothing effects on the mucosa. Hot wet towels to the abdomen, as well as hot daily baths, when possible, are healing and soothing. It is important to instruct all diarrhea patients to bathe daily. A heavy towel is placed on the bottom of the tub so that actually a hot compress is maintained to the perirectal tissues throughout the duration of the bath. Short wave therapy to the abdomen will often relieve cramps and promote healing.

And finally, the patient suffering with diarrheal disease requires physical and mental rest because of the great loss of fluids and nutrient, and the peculiar effect of the diarrhea upon the mental state of the patient. Physical rest does not mean sitting and listening to the radio. It means lying flat on the back, with arms completely relaxed and preferably eyes shut. This position should be maintained from one-half to one hour before and after each meal, depending upon the severity of the diarrhea. It is well known that the bowel is least active when the patient is in the reclining position. Physical rest also means a patient in slow motion: slow in arising, slow in walking, and slow in all activities of the day.

The diarrhea patient must be taught a new philosophy of living. He must be told to avoid over-stimulating his nervous system by excessive environmental contacts. The author tells him in possibly crude, but sincere, manner to "mind his own business", not his brother's, or his sister's; not his friends' or neighbors', but only his own affairs. He must not be a commentator of social, political or military subjects, for fear of inviting disagreement, debate and, nine out of ten times, aggravation. He must be told that worry, fear, anxiety, over-work or loss of sleep will stimulate the muscular components of the bowel and lead to more frequent evacuations. He must be taught the physiologic fact that emotional excitement will inhibit the function of the mucosal glands, thus drying up his stomach and intestinal secretions. This will cause much of the food to be improperly digested, leading to flatulence and more diarrhea.

Beaumont, as long ago as 1833, observed that fear, anger or anxiety have a marked depressing effect on gastric secretion and digestion. The work of Pavloff, Cannon and Alvarez, as well as others, have definitely shown that the emotions have a remarkable influence in changing the function of the digestive system. It is, therefore, important to instruct the patient to avoid all sorts of worry and annoyances, to isolate his or her mind from the so-called "modern life", so that the economic and social stresses surrounding him will not affect his digestion. Re-education of the patient's habits of living, working and thinking will go a long way towards securing that precious physical and mental rest so vital in the management of these cases.

To sum up, physical and mental rest means regular meals, regular hours of sleep, normal and minimum amount of work, regular afternoon naps, and no arguments or discussions. The patient must not be a "NO" man; he must learn to be a "YES" man.

Foci of infection or co-existing infection must be eradicated during remissions. The swallowing of bacteria or absorption of their toxins may induce a relapse. The tonsils, teeth, sinuses and genito-urinary system must be investigated when a patient is slow in responding to therapy or relapses shortly after therapy. A chronic low grade focus of infection may sometimes be the resisting factor to successful treatment.

The author also wishes to emphasize the truism that two heads are better than one. When one has examined the patient, determined the cause of the diarrhea, and instituted appropriate treatment, he must beware of a double disease process if the patient does not show some improvement within two or three weeks. Whatever the associated condition may be, it is advisable to call a colleague in consultation to re-examine the patient and discuss further management of the case. It is not at all uncommon to find a patient suffering with a bacterial diarrhea complicated by a malignant neoplasm of the colon. The patient may have a diarrhea caused by a double infection with bacteria and protozoa. In such a case treatment must include anti-protozoan drugs in addition to the anti-bacterial measures.

Diet for Diarrheal Patients

<i>Breakfast 8:00 A.M.</i>	<i>Lunch 12:30 P.M.</i>	<i>Supper 6:00 P.M.</i>
Orange juice	Tomato or grape-fruit juice	Tomato or grape-fruit juice
Cereal	Meat or fish	Meat or fish
One or two eggs	Two well cooked vegetables	Two well cooked vegetables
Two slices white toast with butter	Two slices white toast with butter	Two slices white toast with butter
Half-glass evaporated milk flavored with half-glass of tea, or postum	Dessert	Dessert
	Evaporated milk as above	Evaporated milk as above

In-Between Meals—10:00 A.M. - 3:00 P.M. - 9:00 P.M.

Bananas, cottage cheese, cream cheese, hard boiled eggs, salted crackers, grilled American cheese on toast, evaporated milk as above.

Cereals: Farina, Cream of Wheat, Puffed Rice, Cornflakes, Oatmeal, strained.

Meats: Beef, Lamb Chops, Steak, Liver, Chicken or Fish.

Vegetables: Carrots, Peas (strained), Beets, Stringbeans (strained), Rice (well cooked), Asparagus tips, Baked Potato or Spaghetti.

Desserts (without skins): Pears (cooked or canned), Apricots, Peaches, Baked Apple, Applesauce (strained), Rice Pudding, Junket, Custards, Fruit Jello, Cornstarch Pudding, Plain Cake (toasted), Cookies, Tapioca Pudding.

Vitamin Deficiency Chart Vitamin A Deficiency

Diagnostic Features:

1. Night blindness (nyctalopia)
2. Dryness of conjunctiva (xerophthalmia)
3. Keratinization of epithelial cells in various parts of body
4. Retarded growth and development

- 5. Inability to resist infections
- 6. Hypochlorhydria

Normal Requirements:

5,000 to 8,000 units DAILY

Therapeutic Dosage:

15,000 to 30,000 units DAILY

(Orally in capsules of 5,000 to 20,000 U.S.P. units each)

*Thiamin Chloride Deficiency (Vitamin B₁)**Diagnostic Features:*

1. Anorexia
2. Impaired digestion
3. Hypochlorhydria
4. Weakness, tenderness and pains in legs
5. Burning, numbness and tingling of the extremities
6. Atrophy of muscles
7. Neuritis and Polyneuritis
8. Nervousness and irritability
9. Bradycardia
10. Dyspnea and palpitation
11. Edema
12. Precordial pain

Normal Requirements:

1 to 3 mg. DAILY

Therapeutic Dosage:

10 to 100 mg. DAILY (orally in tablets of 1 to 10 mg. and parenterally in ampoules of 1 mg. or 333 I.U. per 1 cc up to 50 mg. or 16,666 I.U. per cc.)

*Riboflavin Deficiency (Vitamin B₂)**Diagnostic Features:*

1. Burning and itching of eyes
2. Lachrimation—visual fatigue
3. Cracking and maceration of corners of mouth (cheilosis)
4. Glossitis (magenta red)
5. Erosion of mucous membranes
6. Bulbar conjunctivitis

Normal Requirements:

2 to 4 mg. DAILY

Therapeutic Dosage:

5 to 15 mg. DAILY (tablets or capsules of 5 mg. each and parenterally in ampoules containing the entire B complex)

*Nicotinic Acid Amide Deficiency**Diagnostic Features:*

1. Anorexia
2. Glossitis (fiery red)
3. Stomatitis
4. Indigestion; Diarrhea
5. Characteristic dermatitis (sandpaper skin; roughened, scaly, erythematous, pigmented skin)
6. Psychosis
7. Fatigue
8. Insomnia
9. Achylia
10. Urethritis

Normal Requirements:

10 to 25 mg. DAILY

Therapeutic Dosage:

150 to 500 mg. DAILY (orally in tablets of 50 to 100 mg. each and parenterally in ampoules of 10 to 50 mg. per cc.)

*Ascorbic Acid Deficiency (Vitamin C)**Diagnostic Features:*

1. Petechial and superficial hemorrhages
2. Soreness of joints
3. Bleeding from gums, nose and mouth
4. Weakness and fatigue
5. Decay and loosening of teeth
6. Fragility of bones
7. Anemia
8. Delayed healing of wounds

Normal Requirements:

25 to 50 mg. DAILY

Therapeutic Dosage:

150 to 1,000 mg. DAILY (orally in tablets of 50 to 100 mg. each and parenterally in 2 cc. ampoules of 100 mg. each)

Note: 1) Vitamin D is usually included routinely with Vitamin A. It aids in regulating calcium and phosphorus metabolism.

2) Vitamin K is essential for normal clotting of blood. The author has found it beneficial in many cases of bloody diarrhea.

BIBLIOGRAPHY

1. Alvarez, W. C.: Introduction to Gastroenterology, Paul B. Hoeber, New York, 1939.
2. Bargen, J. A.; Victor, Sister M.: Diet in Intestinal Disorders, J. A. M. A. 97:151-153 (July 18) 1931.
3. Beaumont, W.: Experiments and Observations on the Gastric Juice and the Physiology of Digestion, F. D. Allen, Plattsburg, 1833.
4. Bereovitz, Z.: The Treatment of Food-Borne Diseases of the Gastrointestinal Tract, N. Y. State J. Med. 1450-1455 (July 15) 1941.
5. Bernheim, A. R.: Calcium Need and Calcium Utilization, J. A. M. A. 100:1001-1004 (April 1) 1933.
6. Cannon, W. B.: Bodily Changes in Pain, D. Appleton & Co., 1929.
7. Fradkin, W. Z.: The Control of Rectal Bleeding in the Convalescent Ulcerative Colitis Patient, Jour. Lab. and Clin. Med. 22:896 (June) 1937.
8. Inberman, S. I.: Scurvy Following a Restricted Diet in Colitis, J. A. M. A. 94:1757 (May 31) 1930.
9. Lieb, C. W.: The Effects on Human Beings of a Twelve Months' Exclusive Meat Diet, J. A. M. A. 93:20-22 (July 6) 1929.
10. Moschowitz, E.: Hypoproteinemia, J. A. M. A. 100:1086-1091 (April 8) 1933.
11. Pavloff, J. P.: The Work of the Digestive Glands, Translated by Thompson, W., London, 1910, Ed. 2.
12. Salerno, E. V.: Short Wave Irradiation in Treatment of Inflammation, Prensa Medica Argentina, Buenos Aires, 23:2563 (Nov. 11) 1936.
13. Widdowson, E. M.; McCance, R. A.: Iron in Nutrition, J. Hygiene, London 36:13 (Feb.) 1936.
14. Witts, L. J.: Therapeutic Action of Iron, Lancet 1:1 (Jan.) 1936.

Sulfanilamide-Experimental Production of Liver Damage: Its Effect On Gastric Acidity

By

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IT HAS been generally known that sulfa drugs may cause hepatitis; this clinical observation has been reported by Hageman and Blake (1), Saphirstein (2), Long (3), Banniek, Brown and Foster (4), Garvin (5) Cline (6), Fitzgibbon and Silver (7) and many others. There are several individual reports of autopsy studies on liver tissue in patients who have received sulfanilamide. Berger and Applebaum (8) described early degenerative changes in liver of a patient who had taken only 20 grams of sulfanilamide. Fragerman and Gotto (9) also reported having observed degeneration of liver cells in their studies. Cline recorded autopsy findings of acute yellow atrophy which had occurred after administration of 45 grams of sulfanilamide.

Machella and Higgins (10) attempted to answer this question experimentally by administering sulfanilamide to rats—they report that 30% of the livers of rats on sulfanilamide demonstrated foci of necrosis and that 25% of the livers of rats receiving no sulfanilamide demonstrated similar microscopic changes.

Cannon (11), on the other hand, reports hydropic degeneration of hepatic cells of the livers of two dogs following ingestion of diethylene glycol—(Elixir of sulfanilamide).

In order to obtain additional information relative to liver damage produced by sulfanilamide, an experimental study was instituted using dogs.

PROCEDURE

Dogs (female) were used for these experiments: The experiment was performed as follows: The sulfa drug, 60 grains of sulfanilamide three times weekly, was administered to the dog in the form of a powder admixed with food, masked and offered at an opportune moment to avoid waste. Blood was drawn for chemical analysis: blood levels of sulfanilamide were also determined. Biopsy studies were made of the livers of dogs at various intervals. The gastric juice was collected under histamine by means of a Pavlov pouch, and analyzed frequently for acidity.

The liver biopsies were stained with hematoxylin-eosin, with Sudan III for fat, and Best's carmin for glycogen.

Control studies were made.

Dogs #9181, 8495, and 29 (female) were used, and sulfanilamide administration was omitted. The animals were kept in individual cages and were fed daily at 10 a.m. and allowed to eat at liberty up to 3 p.m. No food was given after 3 p.m. Water was available at all hours. The diet consisted of a mixture of

three parts of Purina Dog Chow Meal and one part Miller's Puppy Meal. A small quantity of freshly ground beef (2 oz. per day) was added as an appetizer. All components of B complex, Vitamin A and D were incorporated in the diet.

The animals were weighed daily and were maintained under proper sanitary conditions.

The liver biopsies and gastric acidity studies were repeated as above.

RESULTS

The results are tabulated under the heading of Liver Study, Gastric Acidity, Blood Level Determinations, Chemical Studies of Gastric Juice and Blood, Microscopic Studies.

Liver Study.—Table 1 presents the results of an experiment in which sulfanilamide was given intragastrically for 2 months, 22 months, 29 months and 40 months, respectively.

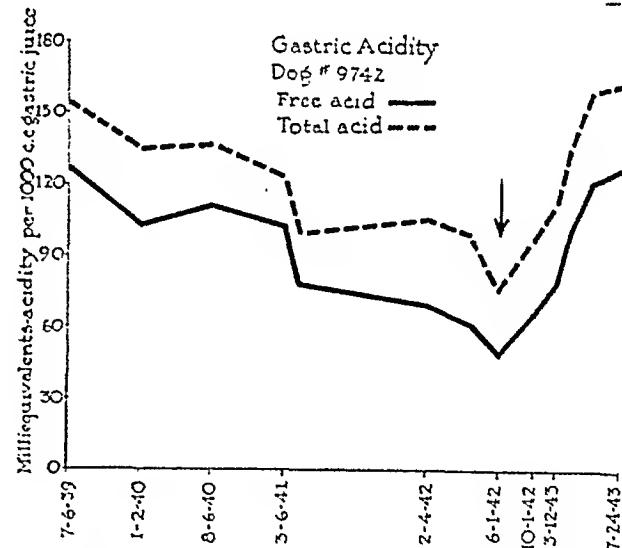


Fig. 1. Behavior of gastric acidity after intragastric administration of sulfanilamide, and after its discontinuance on 10-1-42.

Table 2 presents a list of animals who died from two to fourteen days after intragastric administration of sulfanilamide. Liver biopsies were studied in Dog #7866 who died 72 hours after onset of experiment. The microscopic study is described on Page 269.

In Table 3, an experiment of regeneration is presented in Dogs #9742, #1720 and #6057. Sulfanilamide was administered to these dogs for 40 months, 29 months, and 2 months respectively before it was discontinued. The animals were not given any sulfanilamide for 11 months. Liver biopsies were taken

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at the termination of the experiment.

Gastric Acidity.—In Figures 1, 2 and 3 the response of gastric acidity is presented. A gradual depression of the free and total acidity is noted in all animals and a low level is reached at the termination of the experiment.

Blood Level Determinations.—In Table 4, we present blood level studies of sulfanilamide in mgm. per

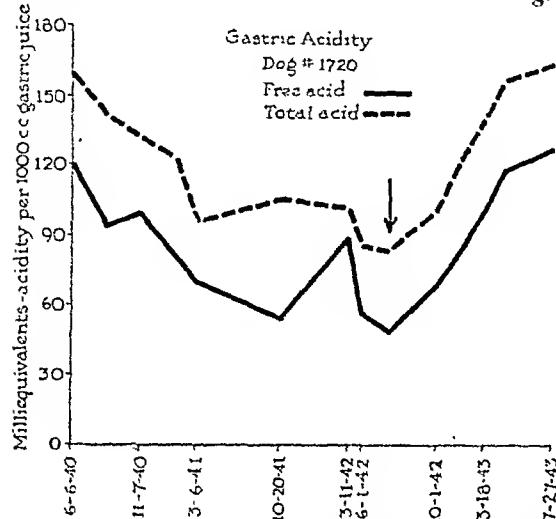


Fig. 2. Behavior of gastric acidity after intragastric administration of sulfanilamide, and after its discontinuance on 10-1-42.

100 c.c. blood—these determinations were made on days when gastric acidities were obtained. Note the red cell counts calculated in millions. The weights of the animals and their general condition is recorded.

Chemical Studies of Gastric Juice and Blood.—These analyses were carried out from June 1, 1939 to August 3, 1943. The values for total base and total

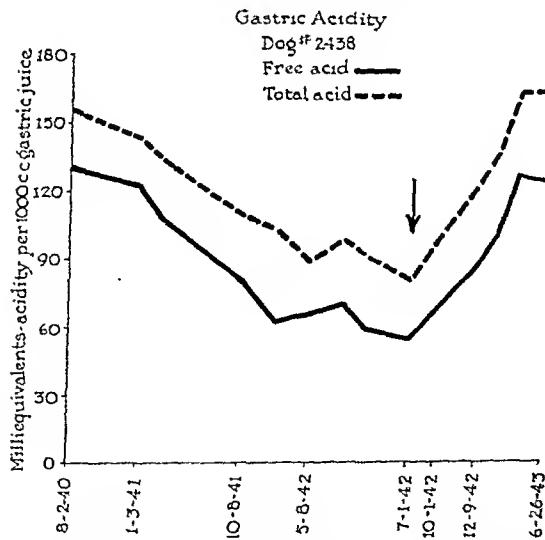


Fig. 3. Behavior of gastric acidity after intragastric administration of sulfanilamide, and after its discontinuance on 10-1-42.

chlorides contributed no additional knowledge to that contributed on following the acidities. The values of hydrogen ion concentrations were non contributory of significant information.

Other Chemical Studies.—The total proteins averaged about 6 grams and the albumin-globulin ratio did not show any inversion. The icterus index was within normal limitations. The fat content calculated per gram of liver averaged 4.0 mg.

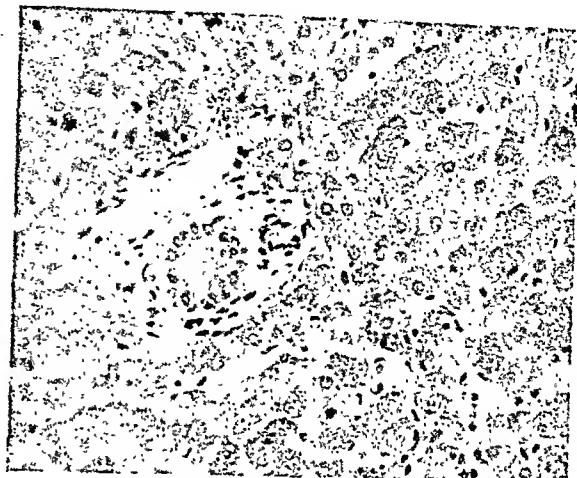


FIGURE 4
Photomicrograph of normal liver tissue.

LIVER

I. Chronic Experiment.

Grossly, the liver was dark red and the surface presented coarse mottling, but not enlarged to a great extent. This finding was exhibited in livers of Dogs #9742, 1720, and #2438 at the terminal stage of the experiment.

Microscopically (October 1, 1942). On hematoxylin-eosin stain the liver slides show proliferation of



FIGURE 5
Photomicrograph of liver tissue stained with H & E, representing advanced stage of a chronic experiment, demonstrating vacuolation, atrophic changes and cystolysis. The nuclei are pyknotic.

vacuolation and evidence of atrophic changes—some cystolysis. The nuclei were pyknotic. The slides stained with Sudan III for fat, show small numbers of fat droplets in the bile duct epithelium and occasional droplet of fat in the liver cells. No evidence of increased amount of fat shown. In comparing slides studied on June 1, 1942 and October 1, 1942, one is

impressed with apparent extension of the infiltrative or degenerative process to the liver cells proper in sections taken on October 1, 1942.

The slides stained with Best's carmin stain for glycogen, show a larger amount of glycogen present in slide section of June 1, 1942 and a relative decrease of glycogen in slide of October 1, 1942.

II. Acute Experiment.

Biopsies taken of liver of Dog #7866 at autopsy after oral administration of sulfanilamide for three days, showed a normal average amount of fat and glycogen present.

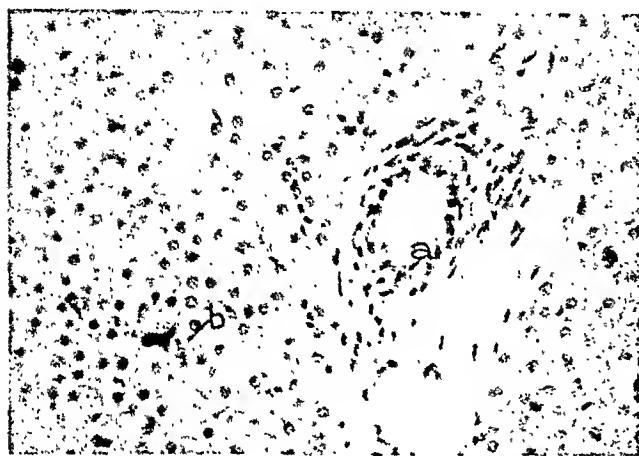


FIGURE 6

Photomicrograph of liver tissue stained with Sudan III for fat, representing advanced stage of a chronic experiment, demonstrating (a) fat droplets in bile duct epithelium, (b) fat droplets in liver cells.

III. Regeneration Experiment.

Eleven months after oral administration of sulfanilamide is discontinued, the liver tissue slides show a return to the normal.

Figure 4 is a reproduction of a photomicrograph of normal liver tissue.

Figures 5, 6 and 7 are reproductions of photomicrographs of liver tissue representing advanced stages of a chronic experiment, stained with H and E, Sudan III and Best's carmin, respectively.

DISCUSSION

Gilman (12) states that during the course of or subsequent to sulfanilamide medication, an acute hepatitis with jaundice and decreased liver function may develop. The damage to the liver cannot, in all instances, be attributed to sulfanilamide but there is indisputable clinical evidence that in certain patients, the drug may cause hepatic injury. The cause is unknown and apparently bears no relation to dosage, type of infection or prior status of liver function.

Watson and Spink (13) thought that the administration of sulfanilamide in the usual doses is followed by some evidence of dysfunction of the liver, such as urobilinogenuria, elevation of the serum bilirubin or outspoken jaundice.

Bannick (14) and his associates, on the other hand,

maintain that the reason hepatitis develops among some patients was that their livers had been damaged prior to the administration of sulfanilamide and the drug caused the pre-existing hepatic damage to progress to a stage from which regeneration was impossible.

Peterson (15) and his associates state that in patients with acute hepatitis associated with bacterial infections, sulfonamide therapy was beneficial and leads to improvement in hepatic function. In patients with chronic damage to the liver, hepatic dysfunction was not aggravated by administration of sulfa-thiazole or sulfadiazine.

The researches of Machella and Higgins (10), show that the livers of rats receiving sulfanilamide were large in animals which received less toxic doses and that the livers were smaller when larger amounts of the drug were given. The livers of dogs in our experiments did not increase in size after oral administration of 60 grains of sulfanilamide, three times weekly over a period varying from two days to forty months. Cannon, in studying the pathologic effects of elixir of sulfanilamide in two dogs, reported that the livers were mottled, but not greatly enlarged; the animals died after ingestion of varying amounts of sulfa material. He reports fatty changes and areas of hydropic degeneration. The necrosis of liver cells is not severe, although there is some shrinkage of nuclei, pyknosis, and nuclear fragmentation.

Microscopic studies made by Machella and Higgins demonstrated foci of necrosis in 30% of the livers of rats to which sulfanilamide has been administered in varying doses over varying periods of time. On "H & E" stain, the foci contain histiocytes, fibroblasts, lymphocytes, but none disclosed presence of stainable fat. Similar foci of necrosis were demonstrated in

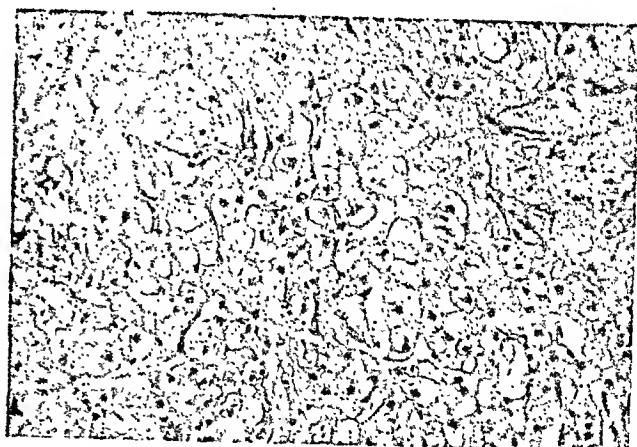


FIGURE 7

Photomicrograph of liver tissue stained with Best's carmin for glycogen, representing advanced stage of a chronic experiment demonstrating marked decrease of glycogen within liver cells.

five rats when sulfanilamide was withheld.

The microscopic report of an autopsy performed by Berger and Applebaum (8) confirm the findings of Cannon.

Machella and Higgins substantiate the findings we made in our experiments in that they suggest that the hepatic cells were enlarged, that the nuclei were pyknotic, and that the cytoplasm stained a faint pink on "H & E" and was vacuolated. On Sudan III we also find small and large droplets of fat in the central and mid-zones.

We find very little fat deposited in the livers of our dogs at the extreme stage of the experiment, and comparatively a negligible amount of fibrosis; this would imply that the amount of fat in the livers remained unchanged. Chemical determinations of fat content

rate of intake (60 grains, three times weekly). The drug was administered to 11 dogs for periods varying from 2 days to 40 months. Four animals survived for a period of 2 months to 40 months while 7 animals survived only 2 to 14 days.

Grossly, there is no evidence to show that the liver damage observed in these experiments can be ascribed solely to toxic absorption of sulfanilamide. The microscopic study of the liver of Dog #7866, who died after a single dose of sulfanilamide showed no evidence of liver damage. The fact that a comparatively large number of animals died within a short time with-

Table 1—Liver Studies - Chronic Experiment

DOG NO.	DURATION OF EXPERIMENT IN MONTHS	LIVER BIOPSIES					
		H and E*		SUDAN III		BEST'S CARMIN	
		6-1-39	10-1-42	6-1-42	10-1-42	6-1-42	10-1-42
9742	40	N	VA	FB	FBL	G++	G+
1720	29	5-20-40	10-1-42	6-1-42	10-1-42	6-1-42	10-1-42
		N	VA	FB	FBL	G++	G+
2438	22	8-20-40	6-1-42	6-1-42	10-1-42	6-1-42	10-1-42
		N	VA	FB	FBL	G++	G+
6057	2	8-19-42	10-21-42	8-19-42	10-21-42	8-19-42	10-21-42
		N	V	FB	FBL	G++	G+

N—indicates that slide is representative of normal liver tissue.

VA—indicates vacuolation and atrophy.

G—indicates the presence of glycogen.

FB—indicates presence of fat in bile ducts.

FBL—indicates presence of fat in bile ducts and liver cells.

H & E—indicates hematoxylin—eosin.

per 1 gram of liver tissue in our experiments varied from 3.8 mg. to 4.6 mg.

The cause of hepatitis following sulfanilamide have been considered as another example of drug hypersensitivity (idiosyncrasy) or due to inherent toxicity.

The evidence in our experiments points to the theory of idiosyncrasy because in the acute experiment, (Table 2) many of our animals died after a single dose (60 grains) of sulfanilamide, while others survived for a period of 40 months at an equivalent

out showing gross evidences of liver damage, might mean that the toxic effect was on some other organ or if it was on the liver, sufficient time did not elapse to allow morphological changes to occur. The picture produced in these experiments is similar to the description of experimental hepatic injury produced by Gyorgy (16) in rats. He states "that the degenerative and necrotic changes in the liver of rats kept on special rations resemble, in location and character, the acute and precirrhotic manifestations seen in various

Table 2—Liver Studies - Acute Experiment

*Dog No.	Date	Period of Survival
12	11-17-39	2 days
14	12-10-39	4 days
15	1-6-39	13 days
17	1-31-39	14 days
18	1-31-39	7 days
20	9-1-40	6 days
7866	8-1-43	3 days

*The dogs listed died from 2 to 14 days after onset of experiment.

kinds of poisoning particularly that due to carbon-tetrachloride. Gyorgy claims that the pathologic picture described for carbon-tetrachloride would apply to other hepatotoxic chemicals as well."

In our experiments with carbon tetrachloride much more fibrosis was evident and the distribution of the damage to the liver was more uniform. Our present experiences resemble the results we obtained with irradiation of the livers of dogs, particularly as to the phase of liver regeneration based on the relative amount of toxic absorption.

The gastric acidity studies in these experiments are interesting, in that the reactions of both free and total acidities are parallel to our experiences in similar studies with irradiation of livers on dogs (17). In the present experiment, there is a decrease in the free and total acidity. The disturbance in the secretory mechanism was apparently parallel to the degree of toxic absorption. As we proceeded with further administration of sulfanilamide, the depression in the secretory mechanism was more pronounced. This disturbance remains until the liver is repaired.

That the disturbance in the secretory mechanism is not permanent and is relative to the degree of liver damage, is demonstrated by the fact that the acidity curves return to the original level when the liver tissues show signs of return to normal, (Table 3 and Figures 1, 2 and 3) or eleven months after sulfanilamide is discontinued.

The fact that the gastric acidities returned to the original level would also imply that the liver has undergone adequate regeneration after sulfanilamide was discontinued.

Table 3—Liver Studies - Regeneration Experiment

DOG NO.	DURATION OF EXPERIMENT		LIVER BIOPSIES					
			H and E*		SUDAN III		BEST'S CARMIN	
			10-1-42	8-1-43	10-1-42	8-1-43	10-1-42	8-1-43
9742	11 mos.	40 mos.	VA	N*	F+	F+	G+	G+++
1720	11 mos.	29 mos.	VA	N	F+	F+	G+	G+++
6057	11 mos.	2 mos.	VA	N	F+	F+	G+	S Digest. G+++

*N → indicates that slide is representative of normal liver tissue.

VA — indicates vacuolation and atrophy.

S — indicates digestion of glycogen in portion of slide previous to staining by saliva.

G — indicates presence of glycogen.

F — indicates presence of fat.

H & E—indicates hematoxylin—eosin.

The results in the control studies were essentially negative—the microscopic studies of the liver pre-

Table 4. Blood Level Determinations of Sulfanilamide

Dog No.	Date	Weight in Lbs.	Condition of Dog	MGM. G. in 100 c.c. Blood	Red Blood Cells in Millions
9742	1- 2-40	24	Good	6.8	6.45
	8- 6-40	24	"	7.4	6.21
	3- 6-41	24	"	6.30	
	2- 4-42	23	"	6.8	6.80
	6-26-42	25	"	7.4	6.35
1720	11- 7-40	25	"	6.5	6.90
	3- 6-41	26	"		
	10-20-41	26	"	7.0	
	3-11-42	24½	"	6.4	6.40
2438	6-15-42	25	"	6.8	6.85
	1-23-41	25	"	7.8	6.60
	10- 8-41	25½	"	7.6	
	5- 8-42	30	"	6.5	6.80
	7- 1-42	29	"	8.6	6.90

sented no changes and the gastric acidities remained unchanged.

CONCLUSIONS

- Microscopic changes were noted in the livers of dogs after intragastric administration of sulfanilamide; Grossly the livers remain unchanged.
- The changes noted in the cellular elements of the liver were atrophic in nature.
- The amount of fat in the livers of our dogs remained unchanged; A definite decrease of glycogen is noted after prolonged intake of sulfanilamide.
- Evidence in our experiments points to the theory of idiosyncrasy.
- There is a definite depression of gastric acidity.
- Progressive damage to the liver depresses the gastric secretory mechanism and is relative to the degree of damage to the liver.

I wish to thank Dr. Robert W. Keeton, Head of the department of medicine, University of Illinois, for his helpful suggestions and guidance in this work. I also wish to thank Dr. Otto Kampineier, Dr. R. Krehbiel, Dr. A. Kendrick and Dr. A. Nedzel for their assistance.

REFERENCES

- Hageman, P. O., and Blake, F. G.: A specific febrile reaction to sulfanilamide: Drug fever. *J.A.M.A.* 109:642, 1937.
- Saphirstein, H.: Hepatitis and toxic erythema with desquamation due to sulfanilamide. *Urol. & Cutan. Rev.* 42:101, 1938.
- Long, P. H.: The clinical use of sulfanilamide and its derivatives with special reference to their possible toxic effects. *Ohio State M. J.* 34:977, 1938.
- Bannick, E. G., Brown, A. E., and Foster, F. P.: Therapeutic effectiveness and toxicity of sulfanilamide and several related compounds. *J.A.M.A.* 111:770, 1938.
- Garvin, Curtis F.: Toxic hepatitis due to sulfanilamide. *J.A.M.A.* 111:2283, 1938.
- Cline, E. W.: Acute yellow atrophy of the liver following sulfanilamide medication. *J.A.M.A.* 111:2384, 1938.
- Fitzgibbons, P., and Silver, B.: Necrosis of liver (case), California and west. *Med.* 50:123, 1939.
- Berger, S. A., and Applebaum, H. S.: Toxic hepatitis due to sulfanilamide. Report of a fatal case with histopathologic findings in the liver. *J. of Lab. and Clinical Medicine* 26:785, 1940.
- Kapnick, I., Hewart, John D., and Lyons, Champ.: Plasma prothrombin and liver function during sulfonamide therapy. *The New England Journal of Medicine* 227:944, 1942.
- Machella, T. E., and Higgins, G. M.: Does sulfanilamide induce necrotic lesions in the liver. *Proc. staff of Mayo Clinic* 16:174, 1941.
- Cannon, Paul R.: Pathologic effects following the ingestion of diethylene glycol. Elixir of sulfanilamide massengill synthetic elixir of sulfanilamide and sulfanilamide alone. *J.A.M.A.* 109:1536, 1941.
- Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, New York, 1941. The Macmillan Co.
- Watson, C. J., and Spink, W. W.: Effect of sulfanilamide and sulfapyridine on hemoglobin metabolism and hepatic function. *Arch. Int. Med.* 65:825, 1940.
- Bannick, E. G., Brown, A. E., and Foster, F. P.: Therapeutic Effectiveness and Toxicity of Sulfanilamide and Several Related Compounds. *J.A.M.A.* 111:770, 1938.
- Peterson, O. L., Deutsch, E., and Finland, M.: Therapy with sulfonamide compounds for patients with damage to liver. *Arch. of Internal Medicine* 72:594, 1943.
- Gyorgy, Paul: Experimental hepatic injury. *Amer. Jour. of Clinical Pathology* 14:67, 1944.
- Streicher, M. H.: Effect of hepatic damage on gastric acidity. *Archives of Surgery* 43:74, 1941.

Allergy as a Factor in Surface Ulcers, Varicose Veins, Phlebitis and Thrombosis

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TO LUMP together so diverse a group of conditions as those indicated in the title of this discussion, might seem at first glance, an invitation to confusion. However, it is my purpose to show, through a brief review of the etiology of each, together with a group of pertinent case reports from my own prac-

tice, that, in some instances, there almost certainly is a definite relation amongst all of them.

VARICOSE VEINS

Various etiological factors contribute to the development of varicose veins. Beside those mechanical con-

ditions which interfere with venous circulation, thereby increasing pressure within the vein, we find lessened resistance of the walls and valvular insufficiency, which may be either of congenital origin or secondary to some inflammatory condition. In the latter case, nutrition of the venous tissue itself is impaired, leading to dilatation and insufficiency. Usually several of these factors combine, following and aggravating one another.

Some parts of the affected vein may be practically normal, at the same time that the muscular and elastic elements of other parts have been entirely replaced by fibro-cicatricial tissue, while still others show a wall that is thin and atrophic. The vein will be more or less adherent to surrounding structures, due, partly to nutritional disturbances, partly to inflammatory changes in the perivascular tissues. Slowing of the flow of blood, together with proliferation of the intima, predispose to development of thrombosis. If the thrombi become calcified, vein stones or phleboliths, will form.

Varicose veins are most common in individuals in their middle years. Multiple pregnancy, pelvic tumor and occupations requiring much standing, are the chief causes at this time of life. Younger persons are affected who have a congenital weakness of the vein walls.

The most common type of varicose veins, is hemorrhoids. Next in frequency come those of the lower extremities, both superficial and deep.

The results vary in both character and gravity. Circulatory and nutritional disturbances are most pronounced when it is the veins of the legs which are affected. Here the skin will become thin, red, atrophic. Susceptibility to any sort of infection or injury is greatly increased, and such conditions heal slowly or not at all. Necrosis, varicose ulcer, eczema and thrombophlebitis are frequent. Varying degrees of edema follow the passive hyperaemia, leading to gradual thickening and induration of the skin and subcutaneous tissues. Weakness or easy fatigue of the legs are common, due, in part, to the circulatory disturbances, in part, to fibrous myositis with secondary degeneration of the muscle fibres.

The most dangerous complications are the thrombophlebitis already mentioned and hemorrhage.

VARICOSE ULCER

Impairment of the venous circulation, due to valvular insufficiency, alone is not enough to cause necrosis of the skin. However, in the related changes in the tissues, the regenerative powers of those tissues are so reduced that any break in the continuity of the surface —any contusion, abrasion, infection, even a small scratch—instead of healing, tends to spread and form an ulcer. This is especially likely to occur in the region of the malleoli and the anterior surface of the tibia—the area drained by the long saphenous vein. In addition, there are other predisposing causes; infiltration of the blood into the tissues following the bursting of a varix, infection of the skin secondary to suppuration

of a thrombus, hyperaemia associated with a furuncle. Each of these can impair the venous circulation still further. Whenever any of these occur, necrosis, limited and superficial at first, later extends into the typical varicose ulcer. Once formed, these ulcers are extremely difficult to heal, and frequently recur, even when some degree of healing has been secured.

The causes of such persistence or recurrence may be simply the same impairment of circulation from excessive walking or long standing that produced the original condition. The small veins, already distended with blood, rupture, causing little hemorrhages into the floor of the ulcer, or into the delicate, new scar tissue, as the case may be. Necrosis and recurrence or extension of the ulcer follow. If bacterial infection also occurs, the ulcer becomes rapidly larger and deeper. Inflammatory hyperaemia may also act in the same way as bacterial toxins, leading rapidly to stasis in and thrombosis of the inflamed vein.

THROMBI

The formation of a thrombus is usually the result of an injury to a blood vessel. It may follow either compression or dilatation of the vessel, or trauma. Invasion of the vessel by infection or disease may result in thrombosis. Or any other factor, interfering with circulation, may have a like effect.

As long as the endothelium remains intact, retardation of circulation alone probably would not result in the formation of a thrombus. However, let any pathological change in the endothelium occur, such as inflammation, degeneration, calcification, or the mere invasion of bacteria, and coagulation is immediately greatly favored. Bacterial toxins, such as, for example, those of puerperal sepsis, in the blood stream, offer most favorable conditions for thrombosis. Although, according to Aschoff (1), it is generally admitted that coagulation must in some way be increased in order to permit fibrin to form, the existence of increased coagulability is not the first stage of thrombosis. However, coagulation of fibrin seems inevitably to follow thrombosis from whatever cause.

This is explained by Dietrich (2) as the result of a sensitization of the endothelium followed by a direct reaction between it and the blood to form the thrombus. Experimentally, sensitization of an organism has been seen to result in foci of endothelium proliferation.

Pfeiderer (3), discussing the increase of embolism and thrombosis in Germany after the first World War, hazards the opinion that sensitization to various foods, to alcohol or to tobacco, may be a predisposing factor. He regards these as of more etiological importance than infections.

Kneppar and Waaler (4) found the results of animal experimentation tended to confirm this stand, regarding the importance of allergies.

ALLERGY

In defining allergies in general, the most reasonable hypothesis seems to be that such disturbances are the

manifestations of stimulation or depression of cellular activity. We recognize such an alteration of normal function as a "crisis"—a reaction or symptom-complex related to some definite causal factor. It may occur in any part of the system.

It is well known that eczema is caused by sensitization of the skin to foods, animal emanations, pollens, clothing, chemicals and many other substances. In these cases, the skin acts as a shock system. Foods reach the skin through the circulation. Why, then, should not the blood vessels themselves also act as a shock system? If the epithelial tissues react to these substances by producing eczema, is it not reasonable to suspect that inflammation of the endothelium, with attendant reactions in the muscular and elastic tissues of the vessel walls, might not be of similar origin in some cases?

That such is a definite possibility is borne out by my experience with the six cases which follow:

CASE I.

Male, aged 67.

January 31, 1935. Symptoms first noticed 3 years before, after walking against a strong wind. Pain of increasing severity, left side of chest, left shoulder, also down arm sometimes as far as wrist; "smothery feeling," usually at 3 to 4 A. M., lasting 15 minutes; pain when getting out of bed; dull pain and shortness of breath upon climbing stairs or following any excitement or exertion; "gas", with, occasionally without, pain. Varicose veins and ulcers past 27 years, both legs, worse on left leg. Had used bandages for 6 years. At age 27, had had varicose mass removed from abdominal wall just above symphysis pubes which weighed 2½ pounds.

Examination showed blood pressure, sys. 200/dias. 100. Blood uric acid, 5.6 mgm.; fasting blood sugar, 100 mgm.; tolerance blood sugar, 188 mgm.; urine albumin, pus cells, hyaline casts present. Pulse very irregular. Ulcers, both legs, over and just above internal malleoli; skin, dark mahogany color, with marked thickening and roughness; varicose veins, large and numerous.

Cutaneous tests made, diet planned accordingly.

February 21. Patient reported feeling much better; had had one slight attack of Angina on previous day, following long and strenuous day in court. Blood pressure; sys. 165/dias. 80.

March 4. Patient reported feeling well, no cardiac pain, distress or "gas". Discoloration and ulcers on legs had completely disappeared. Blood pressure; sys. 135/dias. 70.

After being on prescribed diet for three months, bandages on legs were discontinued. However, any use of allergenic foods caused return of pain with marked itching and discoloration of legs, which would be completely relieved by return to prescribed diet.

CASE II.

Female, aged 60.

May 20, 1933. Symptoms first appeared two years

before; itching all over body, marked redness of lower legs, oozing of blood and serum; ulcers, both legs over lower part of tibia and internal malleoli. For 1½ years, patient had been forced to sleep without clothing or covers because of severe burning and itching of whole body. All symptoms were steadily increasing in severity.

Cutaneous tests made and suitable diet prescribed. Within 48 hours, itching and burning on all of body except legs were so nearly relieved that patient could use night clothes and coverings again. In two weeks, itching and inflammation of legs had disappeared. In two months, leg ulcers had completely healed.

Two years later, this patient developed arthritis after getting chilled and straying from her diet. Return to the diet brought about complete recovery. (See, "Changes in Sensitivity to Allergenic Foods in Arthritic Cases," Turnbull; also, "Changes in the System Affected by Allergenic Foods," Turnbull).

CASE III.

Female, aged 53.

January 2, 1930. Patient reported ulcer over left lower inner side of tibia, first appeared in 1915, in bed 1 month; recurred 1918, in bed 1 month; recurred 1921, in bed 2 months; recurred 1928, in bed 2 months. Ulcer healed during each period of rest. 1927, eczema on neck, chest to lower margin of ribs, both arms, backs of thighs. 1900, had had dislocation of left hip upward into ileum, false joint formed; patient had been told ulcer would not heal permanently till femoral head was replaced in acetabulum.

At time of consultation, examination showed ulcer on left tibia; eczema on neck, chest and back with severe itching; considerable gastric distress and "gas".

Cutaneous tests made and diet prescribed. Itching about neck, chest, back and legs relieved in 48 hours. In one week, inflammatory condition in ulcer had disappeared. In 10 days healing had started. In 4 weeks healing was complete, though patient had not rested in bed at any time.

January 11, 1939. Cold of 5 weeks duration with cough for past 3 weeks; rash over neck, chest and left leg. Skin so "itchy" patient could not sleep. Noises in ears "like steam letting off". Pain in left hip. Left leg again ulcerated, considerable induration over lower inner side of tibia and internal malleolus. Marked redness of epiglottis and laryngeal mucosa. Lungs; left posterior, many rales; right posterior, scattered rales, more pronounced over brouchi.

New set of cutaneous tests made and diet prescribed.

January 26, eczema greatly improved, less redness, very little itching. Induration of ulcer and surrounding tissues greatly diminished; ulcer healing. No cough, no rales in lungs.

February 10, no itching, no induration of skin. Ulcer completely healed. No pain in hip.

CASE IV.

Male, aged 42.

January 9, 1931. Ulcer on neck, first at back, later at right side, continuously since 1927. At time of examination, ulcer was $2\frac{1}{2}$ inches across and $\frac{1}{2}$ inch deep. Reported worse in spring and fall. Many types of treatments, including stock and autogenous vaccines, ointments, washes, X-ray and light treatments, had been tried with indifferent success; ulcer would start to heal then break down again.

Cutaneous test made and diet prescribed accordingly.

January 27. Inflammation had subsided; healthy granulations and ulcer healing.

February 15. Ulcer completely healed, first time in over 4 years.

In this case, there appears to have been a thrombosis of the blood vessels supplying the area involved, which in turn, seems to have resulted from a sensitivity to certain foods. When the allergenic foods were eliminated, the thrombosis first, then the inflammation and ulceration resulting therefrom, disappeared.

As an interesting sidelight, it might be mentioned that this patient stated that clams made him "deathly sick", and he had not eaten them for five years. As no reaction to clams was shown in the course of the tests, they were deliberately included in his diet, and he found that he could now eat them without ill effect. He had apparently lost his sensitivity to this particular food during the years he had eschewed them.

CASE V.

Female, aged 56, married.

February 24, 1930. Pain, soreness and sensation of weight in right thigh, began in 1900, had increased in severity for 5 years; walking difficult; patient bedridden much of the time, as only comfortable with leg in horizontal position. "Tired all the time". Amputation had been advised in 1905. No pregnancies. No history of allergy.

At time of examination, patient complained of pain radiating from groin, along inner aspect of thigh and back of knee down entire leg and foot, also extending into sacro-iliac and lumbar regions. Leg "felt as if it would burst", greatly swollen, skin white and glistening with some areas of papillation. Femoral artery and vein felt like hard cord from inguinal region to popliteal space, with extreme tenderness. The existence of pain in the sacro-iliac and lumbar regions seemed to indicate continuation of thrombosis into the pelvis, involving also the iliac artery and vein.

Cutaneous tests given and suitable diet prescribed. In 2 weeks, there was marked reduction in tenderness and cord-like feeling in femoral vessels: tension and induration of skin, also pain and soreness throughout affected area much lessened. Pain in sacro-iliac and lumbar regions almost completely relieved. Therefore, improvement continued steadily until all symptoms had been entirely relieved. Since that time, there has been recurrence of pain and soreness only when the patient eats any forbidden foods.

CASE VI.

Female, aged 65, married.

January 30, 1920. Frequent attacks of precordial pain, "sharp and knife-like", radiating to left shoulder, arm and hand, past 2 years. Most frequently occurred between 2 and 4 in the morning or following any exertion or excitement. Continuous pain, inner side of right leg, worse at night, since 1885, following childbirth; much more past two years. Massage required before patient could get to sleep at night. History of "sick headaches" in childhood. Much passage of "gas" during precordial attacks, not apparently related to eating.

Right femoral vein very sensitive, feeling like hard cord its entire length. Right leg slightly enlarged, skin and subcutaneous tissue thick, indurated and of mottled appearance; numerous varicose veins in lower third of thigh.

Diet prescribed as indicated by cutaneous tests. In 2 weeks, patient was free from precordial pain; pain in leg so diminished that slight rubbing gave complete relief; soreness and swelling entirely gone; varicose veins no longer visible.

June 20. Patient ate salmon, a food to which she was sensitive. Within 5 hours, there was severe precordial distress, accumulation of "gas", swelling of right leg and return of tender, cord-like swelling of veins. Symptoms increased for 24 hours, then gradually subsided. After 5 days of strict adherence to diet, patient was again free from pain, all evidence of venous inflammation had disappeared. It seems probable that such changes as were outwardly visible in the femoral vein, also occurred in the coronary arteries, although not severely enough to cause complete occlusion.

CONCLUSIONS

1. The causes and symptoms of varicose veins, together with their sequelae, varicose ulcer, thrombosis and phlebitis, are reviewed.

2. Attention is called to the fact that

- a) most of these conditions occur most frequently in the legs, but

- b) thrombosis, in particular, while it has been observed in all parts of the body, is more frequent in the coronary and femoral arteries.

3. Allergenic foods and other substances may produce inflammation and other reactions in the endothelium of the blood vessels, in the same way that they produce the more familiar sensitizations of the epithelium.

4. Six cases are cited: 2 had pruritis and eczema; 3 had varicose ulcers of the leg, 1 of the neck; 2 had angina pectoris, showing involvement of the coronary arteries; there were 2 cases of thrombosis of the femoral vessels.

5. In each of the cases described, complete relief of symptoms was obtained by adherence to diets based on avoidance of allergenic foods, as demonstrated by cutaneous tests. In Cases 1, 5 and 6, lapses from the prescribed diet brought on recurrence of symptoms.

REFERENCES

- Aschoff, Ludwig: "Thrombosis", Arch. Int. Med. XII, p. 503, Nov. 1913.
- Dietrich, A.: "Wesen und Bedingungen der Thrombose und Embolie", Klin. Wochenschr. X, p. 54, Jan. 10, 1931.
- Pfeiderer, "Zur Eutholienfrage", Munch. med. Wochenschr.
- Knepper, R. and Waaler, G.: "Hyperergische Ateritis der Kranz- und Lungengefäße bei funktioneller Belastung", Virchow's Archiv f. path. Anat. u. Physiol., CCXCIV p. 587, 1935.

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

HURST, A. AND BASSIN, S.: *Megaesophagus as a cause of mediastinal widening*. (Am. J. Roentgenol., v. 52, p. 298, 1944).

Megaesophagus was noted in eleven cases in mass roentgenographic chest surveys, mainly of rejected draftees. Subjective symptoms were surprisingly few. Even in cases where the esophagus was very enlarged the subject's condition was good. Dilated esophagus is most marked when the cause is "cardiospasm" and much less marked when the stricture is due to either a benign or malignant lesion. Complete roentgen studies should always be carried out to differentiate megaesophagus from congenital anomalies.

In the eleven cases studied (9 men and 2 women) the main diagnostic features as shown by roentgenograms were these: diffuse widening of the mediastinum, apparent widening of the cardiac contour on the right, and obliteration of the cardiophrenic angle by the dilated esophagus. The upper portion of the esophagus would sometimes show a stippled appearance due probably to contrast resulting from the mixture of air with food. If water had been taken before filming, a definite fluid level was always found crossing the tracheal air column at the level of the clavicles. This was not seen in the absence of taking fluid or food.

STOMACH

CANTERO, A.: *Gastric cancer with febrile onset*. (Union Med. Canada., v. 65, p. 148, Feb., 1945.)

In each of the four patients reported here fever was the first sign of illness. Investigation ultimately showed these patients to have gastric cancer. Fever accompanying gastric cancer has been reported previously. In most cases the presence of fever indicates an ulcerated adenocarcinoma. The gastritides may mimic gastric cancer even to the presence of febrile tempera-

ture. Infiltrating cancers of the stomach ulcerate only infrequently, so that fever cannot be depended on for detection. In all patients with questionable symptoms or with fever and no other manifestations there should be carried out a roentgenologic and gastroscopic study.

FREEMAN, H.: *A gastroscopic control of the treatment of gastric ulcer by duodenal feeding*. (Brit. J. Surg., v. 32, p. 303, Oct., 1944).

Diminution in the amount of gastric juice secreted and reduction in its free acidity are believed desirable to achieve good results in ulcer healing. For this purpose it is absolutely necessary that the stomach be at complete rest. The stomach should not be stimulated and all secretions should be neutralized. Absence of an acid secretion from the stomach brings early relief from pain due to stimulation of a hypersensitive neuromuscular mechanism. Complete rest to an inflamed stomach is best assured by the technique of duodenal intubation. Nutrient material may be given intraduodenally so that the stomach is not stimulated. Gastroscopic observations should be made of the stomach at intervals since such control studies are the sole means of determining if healing is complete or delayed, or the ulcer is subject to recurrence. This is also "the only certain way of detecting an early malignant change in a gastric ulcer."

BOWEL

ANDERSON, S. G.: *A statistical survey of appendicitis in children*. (Med. J. Australia, v. 2, p. 567, 1944).

Between 1931 and 1943 there were 55 children, ages under 3 years, and 878 children, ages 3 to 14 years, with acute appendicitis. In the younger group (under 3 years of age) there were complications (abscess or peritonitis) in 75 per cent of the cases and in the older group (3 to 6 years of age) in 30 per cent. In the older

group the first symptom was abdominal pain, in the younger children the first symptom was vomiting. Mortality percentages were 39 per cent in the younger children and 3 per cent in the older. The majority of deaths were due to complications of abscess or peritonitis. Closure of the wound without drainage gave better results so far as infection of the wound is concerned than closure with drainage.

OPPENHEIMER, A.: *Roentgen diagnosis of incipient cancer of the rectum.* (*Am. J. Roentgenol.*, v. 52, p. 637, 1944).

The author finds his technique suitable for visualization of early lesions of the rectum and sigmoid. While the procedure is a little more time-consuming than routine procedures the end-results yield satisfying details which justify the extra time spent.

Thru a small catheter inserted into the rectum small amounts of barium are injected, the desired level being determined by the position of the catheter tip. Spot or oblique films are taken of the rectum. The catheter is then inserted a little higher and the colon filled with barium by the regular enema technique for the purpose of roentgenographic study of the colon.

The advantages of this procedure are the visualization of small extraluminal and intraluminal lesions which ordinarily are obscured by the customary method of mass-filling the rectum with barium.

DUCASSE, E. R., AND SMITH, N. D.: *Colloid carcinoma in anal fistula: report of two cases.* (*Proceed. Staff Meet. Mayo Clinic.*, v. 20, p. 57, Feb. 21, 1945).

The authors describe two cases of colloid carcinoma which appeared in long standing anal fistula. The lesions in both were strikingly similar. The authors believe that the cancer developed secondary to the fistula. The development of cancer in tissues which have been altered by fistula, cicatrices, or hemorrhoids is rare, a point which makes these two cases of interest.

ORITSEMOV, V. N., AND SHIROKOVA, E. M.: *Clinical observations on the course of dysentery in Leningrad during the year 1943.* (*Pediatria (Moscow)*, 1944, p. 43, 1944).

The average mortality in the Karl Liebknecht Hospital was 4.6 per cent. During the year 1943, it decreased as the nutrition of the population improved, being 11.6 per cent in the first quarter of the year and nothing in the last quarter. The age group 0-2 years had an average mortality of 18.6 per cent, that of preschool age 2.5 per cent and no deaths were noted in school age children. The course was chronic and protracted in most of the greatly undernourished children. This group gave the highest mortality. The chronic recurrent form appeared to have a better prognosis and insignificant loss of weight was seen in these cases. They were the carriers of the disease. The acute form did not differ from the cases usually seen before the siege and occurred in fairly well nourished children. Of the cases seen 67.9 per cent belonged to this acute group. 14.7 per cent were classified as chronic recurrent cases. Of these 29.1 per cent had a mild dystro-

phy, 25.9 per cent a moderate and 7.7 per cent a severe dystrophy. The chronic protracted type was seen in 17.4 per cent of the cases with 81.3 per cent of these showing the most severe type of malnutrition, and 31.3 per cent of the group having scurvy. In general, the epidemic was considered to be of the mild type, no Shiga cases being recorded. The changes found at autopsy in the chronic protracted cases showed the dysenteric lesions in the stage of recovery, but profound dystrophic and avitaminotic changes were recorded. The usefulness of the chronic recurrent is stressed and the literature reviewed and discussed.—Courtesy Biological Abstracts.

MEAD, H. S.: *Reverse rotation producing encapsulation of small intestine.* (*Irish Jour. Med. Sci.*, Ser. 6, p. 581, 1944).

At operation the ascending colon was found to cross to the left and the mesentery of the ascending and transverse colon had stretched out to form a sac and completely encase the small intestine.

PANCREAS

CARRINGTON, H., AND COOPER, F.: *Traumatic pseudocyst of the pancreas.* (*J. Tennessee State Med. Assn.*, v. 36, p. 299, Aug., 1944).

The authors preface a fairly typical case of traumatic pseudocysts of the pancreas with a review of fifty-one previously reported cases. Six weeks after a crushing injury to the abdomen, a mass was noticed in the left upper quadrant. Anorexia, weight loss and distension were prominent symptoms. Roentgenologic examination revealed the intestines to be displaced. At operation the tail of the pancreas together with the cyst were removed in toto. Post-operative course was uneventful.

CURR, J. F.: *Complete rupture of the pancreas.* (*Brit. J. Surg.*, v. 32, p. 386, Jan., 1945).

A case of complete vertical division of the pancreas resulting from a crushing wound to the abdomen is presented. Salient points of the case history were the delayed shock and epigastric pain. Treatment was aimed mainly to combat shock by massive transfusion. In addition ligation of bleeding points without removing the detached portion of the pancreas was carried out. A pancreatic fistula developed but healed readily. An interesting observation was made, namely, large amounts of protein stimulated fistulous discharge, while fat and carbohydrate did not.

MILLER, J. M., WIPER, T. B., ROURKE, M., FogERTY, E., AND LAFETRA, J.: *Physiologic observations on patients with external pancreatic fistula.* (*Ann. Surg.*, v. 120, p. 852, 1944).

Three patients with external fistula of the pancreas were studied. Patients with pancreatic fistula under such continuous drainage soon develop low blood plasma-protein levels and low plasma electrolytes. In particular plasma sodium falls to low levels. Sodium bicarbonate and ephedrine are two measures employed for reducing the secretion and so conserve electrolytes.

The pancreatic secretion in these patients was found to continue throughout the day and night and depended on the state of hydration of the patient. In these patients the secretion was stimulated by intravenous administration of physiological saline, 5 per cent dextrose in saline, and histamine.

YOUNG, H. B.: *A case of accessory pancreas in an unusual position complicated by acute necrosis.* (*Glasgow Med. J.*, v. 142, p. 156, 1944).

The signs and symptoms presented by the patient, a man of 36 years, were those of perforated ulcer. Nausea, vomiting, midgastric pain of a stabbing nature passing backward, were experienced for a few weeks preceding admission. At operation an irregular solid mass was found in the gastrohepatie omentum which was not connected to any other organ. This was removed and found to be a tumor containing island cells of Langerhans with an area of necrosis. This mass probably was an accessory pancreas which became infected: the pancreas itself was found to be of usual shape and consistency and apparently not infected.

TROLL, M. M.: *Aberrant pancreatic and gastric tissue in the intestinal tract.* (*Arch Path.*, v. 38, p. 375-380, 1944).

In 3 of 8 cases of ectopic tissue described, this tissue was pancreatic tissue; in 2 of these cases it occurred in Meckel's diverticulum, and 1, the ileum. Gastric mucosa was observed in Meckel's diverticulum 6 times. In 1 case in the series Meckel's diverticulum contained both types of tissue. The 2 instances of aberrant pancreas in Meekel's diverticulum are the twenty-fourth and twenty-fifth cases to be reported. The ease of pancreatic tissue in the ileum makes the twenty-first in the literature. Of the 3 theories on the pathogenesis of the aberrant pancreas and gastric mucosa, the theory that the tissue was transplanted from the original site during embryonic development is believed to be the most acceptable.

LIVER AND GALLBLADDER

HERMOSILLA, D. F., AND SATOMAYO, O.: *Primary liver cancer.* (*Rev. Med. Chile*, v. 72, p. 685, 1944).

In African negroes primary cancer of the liver stands high as the site of location of neoplasms and occurs in high frequency even at an early age. Among the native Chilean population, however, primary cancer of the liver appears relatively infrequently. The authors observed only eight cases during a period of ten years: two sarcomas, two adenocarcinomas and four hepatomas. The clinical and laboratory findings for these cases are presented.

ROBINSON, G. L.: *A study of liver function and plasma volume in chronic rheumatism by means of phenoltetrabrom-phthalein sodium sulphonate.* (*Ann. Rheumatic Dis.*, v. 3, p. 207, 1943).

Robinson found the plasma volume to be normal in gout, subacute rheumatism, menopausal periarticular fibrositis and osteoarthritis. The plasma volume was

increased in ankylosing spondylitis as well as rheumatoid arthritis. He termed the four abnormalities of plasma volume, plasma protein, red cell volume and body weight that occur in rheumatoid arthritis, "the hydremic syndrome." Liver function was found to be normal in chronic rheumatic disease by a spectrophotometric acetone extraction method for a determination of bromsulphalein in blood. Gross abnormality in plasma volume was found in chronic rheumatis (rheumatoid arthritis) by the same method. Changes in plasma volume, plasma proteins, body weight and red cell volume in rheumatoid arthritis have been found very roughly in proportion to one another.—Biological Abstracts.

THERAPEUTICS

SAKOVICH, M. S., SHERIDAN, R. B., AND ELEPERIN, E. Z.: *Sulfidine treatment of dysentery in cases of alimentary dystrophy.* (*Pediatria (Moscow)*, v. 1944, p. 50, 1944).

In the group of 46 malnourished children, dysentery was frequently complicated by scurvy, pneumonia, otitis or pyelitis: little constitutional reaction was observed and the course was generally prolonged. Sulfidine therapy was generally ineffective. More than half the patients showed no improvement. The group mortality was 18 per cent compared to three per cent in the well nourished group in 1941. Failure of sulfidine during starvation was attributed by the authors to an increase of products of protein catabolism in the blood.—Courtesy Biological Abstracts.

BENTTIE, J., AND MARSHALL, J.: *The value of sulfur-containing amino acids and casein digest in the prevention of post-arsphenamine jaundice.* (*Brit. Med. J.*, No. 4375, p. 651, 1944).

Liver damage is a common occurrence among syphilites who are undergoing treatment with neo-arsphenamine. This study was an attempt to control the liver damage by administering sulfur-containing amino acids during the treatment period when the incidence of damage is highest (beginning on the 14th week). The various preparations used moderated the severity of the damage and delayed its peak occurrence to the end of the second course of treatment. The incidence of occurrence was not influenced, only the extent or severity of liver damage was decreased. Supplemental treatment with methionine and cystine-reinforced casein digest is recommended as a prophylactic measure in men receiving arsphenamine therapy for syphilis. The authors believe that cystine acts to detoxify the arsenical while methionine benefits the liver by correcting a nutritional disturbance. Since cystine will neutralize the effects of the arsenical, this amino acid should be given conservatively or else the purpose of arsphenamine therapy will be defeated.

SURGERY

GILLIES, J. C.: *Acute intussusception due to inverted Meckel's diverticulum.* (*Brit. J. Surg.*, v. 32, p. 328, Oct., 1944).

Inversion of Meckel's diverticulum as a cause of in-

tussesception is known but is not a frequent occurrence. The present case is in a male child two and one-half years old. Abdominal colic and constipation for three months preceding admission to the hospital were the main features. The colic during the last two weeks increased and there was also occasional vomiting. A large mass could be felt extending from the right iliac fossa to beyond the umbilicus. Operation disclosed the diverticulum which was resected together with the cecum and ascending colon. Recovery was uneventful after a poor showing during the first twenty-four hours.

GORDON-TAYLOR, G.: *Second thoughts on the abdominal surgery of "total" war—A review of over 1300 cases*; (*Brit. J. Surg.*, v. 32, p. 247, Oct., 1944).

In 1942 the author discussed the findings of 610 abdominal casualties in this "total" war. Since then he has added an additional 708 cases. The wounds were those sustained by the armed forces and the civilian population as the result of accidents, projectiles, anti-aircraft fragments, etc. The recovery in the cases reported in 1942 was 51 per cent; in the present series 60 per cent. Injuries to the small intestine were sustained in 276 out of the 708 cases or 39 per cent (previous series: 43 per cent). The percentage recovery was 63 per cent, compared with 47.3 per cent reported in the 1942 series. Exteriorization of the wounded colon is considered the proper procedure and is now advocated by many experienced surgeons. This procedure is particularly useful in dealing with a contused and lacerated colon. The present series had 231 cases of injuries to the large intestine (32.6 per cent) with a recovery percentage of 56 per cent. Included are ninety cases (12.5 per cent) of penetrating injury to both thoracic and abdominal cavities. Interesting is the point that this is almost the same percentage of all abdominal wound cases reported in 1942 (12.7 per cent), during the last war (12 per cent) and in the Spanish Civil War (11 per cent). The recovery rate is about 55 per cent. Prognosis is more favorable when solid viscera are injured since most of the injuries are produced by small fragments. Blood transfusions between ambulance and operating table doubtless was responsible for saving many lives.

ABSORPTION

CARDINI, C. E., AND SERANTES, M. E.: *Absorption of fatty acid from the intestine*. (*Rev. Soc. Argentin. Biol.*, v. 20, p. 132, 1944).

Adult rats were given rations containing known amounts of fats. When olive oil was added to the diet the total fatty acids in the mucosa of the intestine increased to twice control levels. Phospholipid concentrations were not affected greatly. While the concentration of saturated fatty acids in the blood rose faster than the unsaturated, the latter was actually absorbed by the intestinal mucosa more rapidly than the saturated fatty acids. The authors conclude that the various fatty acids are absorbed by the intestinal mucosa at different rates and that some are stored within the mucosa for longer periods of time than others.

PATHOLOGY

KIRK, J.: *Observations on the histology of the choledocho-duodenal junction and papilla duodeni, with particular reference to the ampulla of Vater and sphincter of Oddi*. (*J. Anat.*, v. 78, p. 118, 1944).

The material studied was obtained from 11 humans and 1 adult cat. The humans were 7 adults (autopsy), 2 full-term stillborn fetuses, one 6-month old fetus and one 27-mm embryo. In only one human, the stillborn, was a true ampulla found. Muscle was absent at the ostium. The muscle of bile and pancreatic ducts was continuous with the thickened circular muscle of bowel. Valvular folds of mucosa were found in papilla.

LEBLOIS, C. P., AND SERGEYEVA, M. A.: *Vacuolation of the acinar cells in the pancreas of the rat after treatment with thyroxine or acetylcholine*. (*Anat. Rec.*, v. 90, p. 235, 1944).

Widespread vacuolation of acinar cells in the rat pancreas has been noted after an acute treatment with acetylcholine. This effect has been diminished if animals were previously thyroidectomized and it was greatly augmented if for several previous days they were treated with thyroxine (0.3 mg. daily). In the latter case vacuolation extended to every single cell of the pancreas. The vacuoles appear empty or loaded with various cellular elements: clumps of agglutinated zymogenic granules, masses of cytoplasm including the nucleus itself. The vacuolated areas sometimes showed complete degeneration. Vacuolation was obtained also in normal animals treated with thyroxine alone, although less extensive, than after the combined action of acetylcholine and thyroxine. Since vacuoles first appear among the zymogen granules it is logical to assume that they resulted from activation of the trypsin in situ, finally leading to auto-digestion and degeneration. Some workers on this problem have produced an acute pancreatitis by injections of acetylcholine in the dog. Acetylcholine does not produce these degenerative changes through some action on the thyroid gland, since this drug is effective in thyroidectomized animals. The phenomenon of vacuolation appears to be a result of an increased parasympathetic tonus induced by administration of acetylcholine. Thyroxine increases the ability of acetylcholine to produce vacuolation in the pancreas.—*Biological Abstracts*.

BAKER, FRANK: *Stability of the microbial populations of the caecum of guinea-pigs and rabbits*. (*Ann. Applied Biol.*, v. 31, p. 121, 1944).

The microbial population of the caecum of a one month old rabbit, an adult rabbit and 2 guinea-pigs, respectively, exhibited distinctive features which could be tabulated precisely, and which persisted when the animals were kept in the same cage for 14 days and fed on the same diet. This observation demonstrated that a considerable resistance opposes cross infection. The caecal population was reduced during passage through the large gut which indicated that the distribution and density attained at various levels throughout the alimentary tract by particular members of the mixed microbial population was determined (in each

herbivorous species) by a complex of regional factors.
—Courtesy Biological Abstracts.

EXPERIMENTAL MEDICINE PATHOLOGICAL CHEMISTRY

STETTEN, DE W., AND SALCEDO, J.: *The source of the extra liver fats in various types of fatty liver.* (*Biol. Chem.*, v. 156, p. 27, 1944).

Rats were kept on special stock diets which were either choline-free or contained choline and extra l-cystine. Other experiments were performed on mice receiving injections of anterior pituitary extract when fasting. All the animals in each experiment were also given deuterium oxide (heavy water) as tracer substances. The rats were killed after the fourth day of the experiment and the mice after 96 hours. The livers and carcasses were analyzed for fatty acids and body water. The rats on the choline-free diet had gained less in weight than did control rats (kept on a diet containing choline) but the fatty acids in their livers were higher. About half of the liver fatty acids were synthesized during the experimental period (4 days). The depot fatty acids were laid down in both groups at the same rate during this period. This is interpreted to mean that the fatty acids are synthesized chiefly in the liver and that these do not leave the liver readily when there is a choline-deficiency state. On the other hand, in the rats receiving extra cystine there were found fatty livers but the proportion of fatty acid increase was greater in the depots than in the livers. Probably this was due to excessive synthesis of fatty acids. In mice receiving anterior pituitary injections the livers contained more fatty acids than did the control livers and (in the absence of food) this must have come from depot fat. In fatty liver conditions in the human the fat appears in the liver as the result of migration from body depots rather than new synthesis.

WHIPPLE, G. H., ROBSHIT-ROBBINS, F. S., AND HAWKINS, W. B.: *Eck-fistula liver subnormal in producing hemoglobin and plasma proteins on diets rich in liver and iron.* (*J. Exptl. Med.*, v. 81, p. 171, 1945.)

Chloroform was administered to dogs provided with Eck fistula. Only little liver damage resulted even when the amount of chloroform given was twice that found lethal to control dogs. The ability of the Eck-fistula dog to produce hemoglobin is greatly impaired by intravenous administration of acacia which is deposited in the liver. In experimental conditions of anemia in the Eck-fistula dog, standard diet factors and iron are not utilized as efficiently as they are in anemic control dogs. In such experiments the regeneration of hemoglobin may be only one-fourth of that in normal dogs. Hypoproteinemia induced in Eck-fistula dogs results in a very low production of plasma proteins, sometimes as little as ten per cent of normal being formed.

This study lends support to older studies that the liver is an important site of formation of plasma proteins such as fibrinogen, prothrombin and albumin. It also shows that the liver is concerned in some manner with the production of new hemoglobin. Possibly

the liver is concerned with new hemoglobin formation thru the utilization of the very same plasma proteins which are largely derived from the liver. Failure to produce hemoglobin in these Eck-fistula dogs would thus be interpreted as a malfunction of the liver secondary to failure to produce plasma proteins.

METABOLISM AND NUTRITION

GORDON, HARRY H., AND LEVINE, S. Z.: *The metabolic basis for the individualized feeding of infants, premature and full-term.* (*J. Pediat.*, v. 25, p. 464, 1944.)

The authors report a review of experimental data obtained from metabolic studies which bear directly on the practice of infant feeding. They illustrate their findings by tables showing the relation of water retention to body weight change; urea clearance; effect of varying the amount of dietary fat on the excretion of fat; nitrogen absorption by premature infants; and the average respiratory quotients. They also show charts indicating the effect of changing intake of water balance in premature and full-term babies; approximate energy expenditure of normal, premature, and marasmic infants; excretion of fat by young full-term and premature infants; nitrogen retention by premature and full-term infants and effect of changing intake; effect of human and cow's milk on calcium stores of premature infants; effect of intake of aromatic amino acids on the urinary excretion of intermediary products and effects of vitamin C; and the clinical course, feeding and therapy of a 662 grams infant during first 3 months of life. Their observations suggest the desirability for critical re-elevation of the clinical impression that human milk (which is relatively high in water and fat, and low in calcium, phosphorus, and protein) is the feeding of choice for these subjects.

—Courtesy Biological Abstract.

MISCELLANEOUS

EISENBRANDT, L. L.: *Studies on the pH of saliva.* (*J. Dental Res.*, v. 23, p. 363, Oct., 1944).

Readings on saliva samples were taken one minute after collection of the unstimulated sample. Readings were taken one week each month for a period of one year. Two women and five men were studied.

The mean pH of saliva of the seven subjects was 6.64; this figure is derived from 1552 electrometric readings with the glass electrode. The pH was lowest at 9 A. M. and highest at 5 P. M. Distinct seasonal variations were noted.—R. L. Burdick.

LUFKIN, N. H. AND HODGES, F. T.: *Cadmium poisoning.* (*U. S. Naval Med. Bull.*, v. 43, p. 1273, 1944.)

Cadmium-plated utensils and vessels were used in the galley and there occurred an outbreak of cadmium poisoning. The symptomatology was identical with that of acute poisoning by staphylococcus enterotoxins and required careful work for differentiation. Sodium bicarbonate precipitates cadmium salts and therefore is an excellent substance to use for lavaging the stomach in cadmium poisoning.

High Dosage Vitamin C in Allergy

By

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IN a recent editorial in the Journal of the American Medical Association discussing the anti-spasmodic action of "hypotensive" extracts on smooth muscle, it was pointed out that while many clinical reports on the usefulness of pancreatic extracts existed in the literature, the actual experimental demonstration showed no effect that could not be attributed to the preservatives used in the extracts. The very cogent conclusion was that "the results of these investigations are but another demonstration that clinical results, even though apparently beneficial, are not in themselves a definite proof of the effectiveness of the drug employed. The pharmacodynamic effect of a substance can, with greater accuracy, be demonstrated in properly controlled animal experiments".

It is precisely this situation that has beset the question of Vitamin C in allergy. Clinical data is itself subject to so many uncontrollable factors that at best, they must be considered only as of secondary importance, unless supported by both animal pharmacologic control and physiological rationale.

While clinical observation is simple and subjective, pharmacologic control is expensive, painstaking and objective. Physicians who readily give an opinion on the value or lack of value of Vitamin C in allergy are not so ready to spend a year on animal experimental confirmation to back up their easily arrived at conclusions.

When in June 1938, I published in the Annals of Otology, Rhinology and Laryngology, a paper on Calcium Cevitamate in the Treatment of Acute Rhinitis, I recorded one hundred clinical cases of vasomotor rhinitis associated with the common cold and various allergic states treated with large doses of calcium vitamin C. The allergic patients seemed particularly to benefit. There was at that time no suggested plan of experimental control and years were spent probing various methods. In the meantime, clinical opinion took the usual course of finding subjective proponents and objectors when in 1939, I ran across the technique of Sollman and Gilbert for the microscopic observation of bronchiolar reactions. Here at last was an almost ideal procedure for evaluating the antihistamine effect of Vitamin C as well as the influence of Vitamin C on various anti allergic therapeutic agents.

The technique was difficult and required nine months of special training of a skillful technician. The improvements in procedure and the detailed description was read before the American Chemical Society in 1940. Two years later, Holmes also reported before the same Society, favorable clinical results obtained in the treatment of allergy by large doses of Vitamin C.

During the interim, a rather large literature developed around the detoxifying action of Vitamin C in regard to arsenicals and Bundesen et al showed that Vitamin C applied on patch tests locally to the skin of arsenic sensitive patients, strikingly diminished the allergic reaction to arsenic, whereas the oral administration of Vitamin C did not influence the patch test. Duke University investigators also arrived at the conclusion that oral doses of Vitamin C did not affect the intradermal or scratch test sensitivity. The inadequacy of this type of experimental approach becomes obvious when viewed in the light of Bundeson's work which showed that arsenic sensitivity was reduced by Vitamin C even though the skin test was not affected, except when the Vitamin C was locally applied. Oser and Sulzberger showed that scorbustic guinea pigs were definitely more sensitive to arsphenamine than animals kept on a normal or high Vitamin C.

Unfortunately, we do not today possess a method of testing the immediate requirements of Vitamin C arising under various physiologic conditions. Neither the fragility test nor the saturation test supplies this data. Bronstein showed that adrenalin accelerates the appearance of scurvy and Cannon established the fact that emotions mobilize adrenalin.

The intimate relationship between emotional excitement and allergic reactions is a most common experience, and the increase of Vitamin C requirements likewise become obvious. As yet, we have no method of experimentally demonstrating this relationship other than the antihistamine reaction.

Attacking the problem from a physiological angle, I published a paper on Histamine Adrenalin Balance, pointing out the role of calcium ascorbate.

There remained a further biochemical approach for support of our clinical observations. This was particularly suitable in the study of hay fever reactions since the outstanding clinical feature was the disturbance of tissue fluid balance. The rhinorrhea represents a considerable amount of fluid loss over the period of the hay fever season and simultaneously was the most obvious symptom by which to record improvement.

In studying the mechanism of fluid balance, it was clear that urea formation was the predominantly physiologic factor. An analysis of the biochemistry of urea formation shows the amino acid arginine to be the main source. Through the breakdown of arginine through citrulline and ornithine, we have the urea cycle. It was therefore, startling to find that the antihistamine effect of arginine was independently observed by Landau and Gay. In starting arginine on the urea cycle arginase is

the essential enzyme. Arginase is activated by ascorbic acid and thus we again come to a connecting link biochemically between ascorbic acid and allergy. The diuretic effect of Vitamin C is thus also explained. This diuretic action was also clinically observed by some of the patients and probably plays an important role in the clinical improvement.

The clinical use of Vitamin C in the various intoxications such as lead shown by Marchmont, arsenic shown by Bundesen et al, arsphenamine demonstrated by Oser and Sulzberger are interesting when viewed from the angle that histamine shock shows pathologically similar pictures to that of the intoxications. Moon has brilliantly described the pathologic physiology of these conditions.

Similarly the action of Vitamin C in promotion of wound healing and in the treatment of non surgical illness are intimately related to its antihistamine effect. The bibliography of the papers describing the action of Vitamin C in these conditions numbers well over three hundred. This has been carried to the point where Holman recommends administration of large doses of Vitamin C to all patients entering a hospital for medical or surgical care.

It is therefore not unexpected to find Holmes in 1942 confirming my earlier finding of 1938 that large doses of Vitamin C were beneficial in the treatment of seasonal allergy. In my series of one hundred cases of acute rhinitis and vasmotor rhinitis treated by calcium evitamate, the patients received injections of 3 cc of a 15% solution of calcium ascorbate. The Vitamin C dosage in each injection was 450 mg. In view of the fact that the vitamin was given parenterally, it should be considered as equal to 1000 mg. by month. This dosage produced striking results as shown in my report. However, the pharmacological dose in those days was considered to be 40-60 mgs. So, when I originally presented calcium ascorbate as a therapeutic source of calcium for the program of the American Chemical Society, it was rejected on the basis that a therapeutic dose of calcium ascorbate containing 450 mg. of ascorbic acid was so far above the accepted 40-60 mg. that they could see no basis for admitting it as a therapeutic calcium salt. Today, of course, we know that in tuberculosis and acute infectious diseases, a daily requirement of 1000 mg. is frequent. The United States Pharmacopeia also makes the statement that no toxic dose for man or animal has yet been established.

The dosage of 40-60 mg. of Vitamin C is really a prophylactic antiscorbutic dose rather than a therapeutic dose. Most interesting is the finding of Yoshekawa who showed that the administration of daily doses of 2.5 mg. of Vitamin C while guinea pigs are being allergized will increase the allergy; moderate doses have no effect and large doses, 100 mg. will have an inhibiting influence. This observation is in direct line with my own experience and that of Holmes. Clinical observations therefore on patients receiving small doses of Vitamin C for treatment of allergy, is not to be considered relevant to the question.

The striking difference between the effect of a single large dose and of moderate repeated doses of ascorbic

acid in Vitamin C deficiency was demonstrated by Mouriquand and Edel. They found that a single dose of 50 mg. ascorbic acid doubled the survival time of guinea pigs with developed scurvy. Even 25 mg. had a life prolonging effect. Weekly doses of 10 mg. caused temporary improvement for five weeks followed by a sudden relapse and death. This experimental work throws further light on the discrepancies in clinical reports where small prophylactic doses are compared with the large doses recommended by Holmes and myself.

During the hay fever season in 1944, a special clinical study was made on vitamin C tablets containing in three tablets, a dose of 250 mg. vitamin C and 1 mg. thiamin. Kim and Lee demonstrated that vitamin B during an allergization has an inhibiting effect on anaphylactic shock in guinea pigs.

The patients represented two groups; Group A, those receiving only the special vitamin, and a second group B given the special vitamin tablets and desensitization. As a control, the same patients' condition in 1943 was used. Pollen counts for 1944 and 1943 were recorded during the periods that the patients returned for observation. In general, it was found that patients who felt well, did not take the time to report at the office, so that the follow-up notes were really showing the less favorable days. A general questionnaire was therefore composed to summarize comparative data and the totals tabulated, as follows:

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever?
2. Do you have food allergies as well?
3. Do you have asthmatic attacks during the hay fever season?
4. When did you start taking the special vitamin C tablets?
5. When did you first have any hay fever symptoms?
6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less
 than previous years?
7. How many tablets did you take at the beginning?
8. Did increasing the dosage give
 - a. same
 - b. better
 results?
9. Do you think the special vitamin C tablets were
 - a. no help
 - b. helpful
10. Did the tablets cause any irritation of the stomach?
11. Was there any increase in urination after taking tablets aside from hay fever symptoms?
12. Did you feel generally
 - a. same
 - b. worse
 - c. better
 than previous years?

13. Did you also receive hay fever injections?
14. Have hay fever injections been helpful in previous years?
15. Would you consider the vitamin C tablets modified your hay fever attacks?

Remarks:

Name:

Occupation:

Of the 27 cases studied, 11 patients received simultaneously pollen desensitization. In this group 9 reported that the combination of desensitization plus the vitamin C B tablets was more effective than desensitization alone as received in previous years, thus indicating that they had experienced a beneficial result from the added vitamin C therapy.

Among those receiving only vitamin C B tablets there were 2 who had received desensitization in previous years and had this year received only vitamin C B pills. In this group both reported benefits which were greater than that derived from desensitization in previous years. Twenty showed benefits with vitamin C B pills greater than other previous remedies or any treatment. As a result of this tabulation, we can conclude that group A showed 11 with improvement over previous years. Group B showed 9 with improvement over previous years. In view of the fact that the total pollen count in 1944 was 115% of average, whereas that for 1943 was 88% of average, we can readily see that although 1944 was 27% higher in pollen concentration than in 1943, 74% of patients receiving vitamin C.B tablets felt better in 1944 than they did in 1943.

Similarly in answer to question 12, twenty of the twenty-seven reported feeling better than in previous years giving 74% of improvement for this group.

Question No. 14 which compares the benefit of hay fever injections in previous years, 9 patients had been helped, whereas 14 had not been helped and 3 were having their hay fever for the first season. One patient reported "not much improvement". Question No. 14 is a very revealing one insofar as it indicates a relatively low percentage of satisfactory results from desensitization alone.

Question 15 is still more striking since 24 of the 27 patients felt that the vitamin C B tablets modified their hay fever attacks.

On Question 9, here again 23 of the 27 patients reported vitamin C B tablets were helpful.

On Question 8, a large dosage was started from the very onset in 8 patients. Of the remaining 19 cases, increasing the dosage gave a better result in 12 patients, thus showing that the high vitamin C dosage of 9 tablets a day makes a very definite difference in interpreting clinical benefits. This is in direct conformity with the experimental work cited earlier in this paper as well as the experience of Dr. Holmes and myself in my previous publication of the Use of Calcium Cevitamate in The Treatment of Acute Rhinitis and Allergic Conditions. Virtually all of the 100 cases reported, experienced definite benefit. In that series, vitamin C was given parenterally, each dose representing approximately 450 mg. of vitamin C. The rationale

of the use of large doses of ascorbic acid in upper respiratory disturbances including vasomotor rhinitis and asthma was presented for the first time. This was the first introduction of large dose vitamin C therapy.

Question 10. . . . Six patients indicate that there was some irritation of the stomach ranging from slight indigestion and uncertainty, and one case of hives and irritation of the lids. Twenty-one of the patients complained of no discomfort whatever. None of the patients with the exception of the one suffering from hives felt irritation sufficient to warrant discontinuance of treatment.

In response to Question No. 11, nine of the patients reported an increase in urination during the time of the administration of Vitamin C. This is in itself a difficult question to answer since most patients would not notice an increased urination unless it was something quite definite. Of all these patients reporting an increase in urination, we observe they also reported in question 12 that they felt better than in previous years thus indicating that a diuretic effect was observed in those cases that reported improvement from C B tablets.

In Question No. 7 which indicates the number of tablets used, it was interesting to note that all those patients who were receiving 9 tablets daily, only 2 patients reported any stomach irritation; 1 indicated slight heart-burn; the other slight stomach irritation. Of the remainder reporting stomach irritation were all those who received only 3 tablets daily, thus indicating that it was not the size of the dose which caused the complaint, but rather a special sensitivity to Vitamin C itself. This, of course, can be dependent on whether or not the patient was suffering from some other form of gastric disturbance such as hyper acidity.

In reply to question No. 6 comparing the attacks of 1944 to previous years, we find that 17 patients considered their attacks less than in previous years; 5 considered their attacks the same as in previous years; 1 complained of a worse season than in previous years; 2 were in their first season and so had no basis for comparison; 1 patient stopped treatment early because of sensitivity to Vitamin C, and 1 patient felt the attacks to be somewhat less but severe.

Question 5. The first day of the attack of this season's hay fever was requested in the questionnaire, but was confused with the duration of the hay fever suffering by some of the patients.

Question 3 inquired as to the frequency of asthmatic attacks; 12 of the 27 patients suffered also from asthma. Of these, 8 patients replied in answer to question 12 that they felt better than in previous years; 2 reported worse than last year; 2 reported the same as in previous years. In view of the fact that asthma is a severe disease, it is highly interesting to learn that 8 of the 12 patients showed improvement. This can be considered as a relatively high percentage of therapeutic success for this intractable disease and clinically substantiates the experimental work showing the anti-histamine effect of Vitamin C. Of 8 of the asthmatics benefited, 5 were taking 6 or 9 tablets daily, thus showing that the dosage employed was a vital factor in the therapeutic success.

In further evaluating the benefits of Vitamin C in allergy, it is interesting to note that 14 of the 27 patients suffered from food allergies as well. Of these fourteen, 11 reported in answer to question 12 that they were better than in previous years; 2 were not sure because of the first season; and 1 reported that he was worse this season. This high incidence of general improvement associated with both food and pollen sensitivity is a further indication of the usefulness of Vitamin C, since part of the discomfort of an allergic patient generally is attributed to food allergies current at the same time, particularly in the case of asthmatics.

This survey has thus brought out a most valuable accumulation of data not hitherto surveyed from the critical angle here presented. I have felt that a completely untreated group was unnecessary for control since the average pollen count between the year 1943 and 1944 showed over 25% increased pollen content allowing the conclusion that a completely untreated group would probably show an increased severity of attacks during 1944 as against 1943. It is apparent that patients who are not receiving any treatment at all are unwilling to spend their time coming to the physician simply for observation. The following is a report of the pollen count as taken at the Jewish Hospital of Brooklyn:

Pollen Counts
Ragweed Season of 1943

	<i>August</i>	<i>September</i>	<i>October</i>
1	0	235	2*
2	1	233	4
3	2	106*	3
4	rain	45	4
5	0	61	1
6	0	60	1
7	6	163*	7
8	3*	76	4
9	rain	144	6
10	4*	32	0
11	27	56	1
12	2	34	1
13	rain	20	0
14	39	28*	0
15	25	51	rain
16	28	137*	rain
17	37	12*	0
18	33	22	rain
19	32	18	0
20	66	48	
21	17	5*	
22	32	10*	
23	158	27*	
24	110	7	
25	119	4	
26	142	6	
27	rain	36	
28	98	26	
29	22	19	
30	118	rain	
31	236		
	1357	1721	45

*incomplete count due to showers.

Average total ragweed 1936 to 1943

3,531

Total ragweed for 1943 (July 14 to Oct. 20)

3,115

Total ragweed for 1943 (Aug. 9 to Sept. 28)

3,047

Pollen concentration for Ragweed Season 1943, 88% of average

Pollen Counts
Ragweed Season of 1944

	<i>August</i>	<i>September</i>	<i>October</i>
1	0	106	3
2	rain	346	3
3	rain	354	3
4	3	238	2
5	0	319	1
6	rain	312	1
7	4	455	1
8	3	279	2
9	9	68	0
10	19	50	1
11	26	43	0
12	25	rain	
13	24	rain	
14	29	rain	
15	32	75	
16	4*	19	
17	7*	25	
18	82	16	
19	42	2*	
20	40	10	
21	38*	33	
22	93	16	
23	75	13	
24	75	12	
25	52	9	
26	43	14	
27	51	4	
28	56*	2*	
29	152	11	
30	161	7	
31	131		
	1276	2838	17

*incomplete count due to showers.

Average total ragweed 1936 to 1944 3,599

Total ragweed for 1944 (July 21 to Oct. 10) 4,139

Total ragweed for 1944 (Aug. 9 to Sept. 28) 4,086

Pollen concentration for Ragweed Season 1944, 115% of average

In answer to the remarks, 9 patients made statements relevant to improvement as follows:

Remarked by:

R.F. — "Hay fever attacks vary so widely from day to day that to correlate the effect of the vitamin C with the physical condition is difficult. It was not a complete cure."

E.H. — "I was much more comfortable during this past hay fever period and also had better after effects."

W.L. — "Better general condition."

G.E.P. — "Improvement better than over previous years, but I did not have medical treatment before for same."

S.R. — "Did not take the pills from Sept. 21 to Sept. 28th, and missed them and sneezed during that period."

F.B.S. — "This year the hay fever attacks started later for me than any previous year, namely Sept. 3rd. Also, instead of losing weight during the season, I gained about four pounds."

F.W. — "I have only had about four or five very bad attacks this season due to the vitamin C tablets. I must emphasize the fact that I felt better this season for the first time in twenty-five years."

G.B. — "I definitely believe that the tablets were helpful."

B.B. — "Went without pills one day and had running nose again. Took only two tablets in the evening."

Four indicated reason for lack of improvement as follows:

Remarked by:

M.M. — "I was at the White Mountains for three weeks and had a few light attacks in the morning, but have had two bad attacks since returning."

A.R. — "Due to a bad season I was not as well as the past two years."

A.S. — "I was more exposed to pollen this year because of military training."

S.C. — "Treatment discontinued because of hives."

The remainder made no relevant remarks, but indicated their replies in the preceding questions:

Remarked by:

G.P.C. — "I have had a bad sinus infection. Dr. Ruskin operated on me in February and I have had a series of injections after, until June."

N.H. — "Had dust injections."

M.J.H. — "I started taking the tablets late in the season."

R.R. — "Vitamin C tablets stopped after two weeks. Now taking nucleic acid powder with relief."

B.W. — "Also received dust injections."

R.B. — "For more than a year I have been taking daily doses of combined vitamins."

P.S. — "I took only a few of the tablets."

A much more comprehensive story of the therapeutic effect is evident from the progress notes and history of the cases which follow.

Case I

R. B.

419 E. 57 St.

New York, N. Y.

History

Has had hay fever and asthma for twenty years.

Has had very little benefit from any therapy including desensitization.

Examination

Nasal Mucosa—Hyperplastic

Turbinates — Inferior turbinates hypertrophied

Discharge — Mucoid discharge in both middle and superior meati on both sides
Bilateral hyperplastic pan-sinusitis

Therapy

5/19/44—Allergy testing with 4+ to dust, feathers, ragweed and Timothy.

Started series of catarrhal vaccine and protein injections.

7/4/44—Started C.B. Pills, 1 T.I.D.

7/15/44—No irritation of stomach; an increase of urine.

8/4/44—Less sneezing, probably once a day. 1944 pollen count 0
1943 pollen count 0

8/15/44—Patient states general condition seems better. 1944 pollen count 32
1943 pollen count 25

8/30/44—Patient states he has had fewer attacks, but more severe, causing 1944 pollen count 161 physical exhaustion. 1943 pollen count 118

Clinical Summary

5/19/44—Nasal mucosa moderately hyperplastic; moderate nasal obstruction. No acute signs.

7/4/44—Mucosa engorged, moderate amount of sero-mucinous discharge.

7/15/44—Nasal mucosa moderately engorged, discharge diminished. Nasal ventilation fair.

8/15/44—Nasal mucosa moderately congested; very little nasal discharge; nasal ventilation good.

8/30/44—Nasal ventilation has remained fair; slight sero-mucoid discharge.

1. For how many seasons have you had hay fever? 19 years knowingly, however, no symptoms appeared while on the west coast, (1930-1933).
2. Do you have food allergies as well? Yes.
3. Do you have asthmatic attacks during the hay fever season? Occasionally.
4. When did you start taking the Special Vitamin C tablets? July.
5. When did you first have any hay fever symptoms? Summer of 1925.
6. Would you consider your attacks
 - a. worse
 - b. less
 - c. samemore severe.
7. than previous years?
8. How many tablets did you take at the beginning? 3 per day.
9. Did increasing the dosage give
 - a. same
 - b. better
 - c. worseless frequent, but much results?
10. Do you think the Special Vitamin C Tablets were
 - a. no help X
 - b. helpful
11. Did the tablets cause any irritation of the stomach? No.
12. Was there any increase in urination after taking tablets aside from hay fever symptoms? Questionable.
13. Did you feel generally
 - a. same
 - b. worse X but attacks were less frequent than previous years.
 - c. betterthan previous years?
14. Did you also receive hay fever injections? Yes.
15. Have hay fever injections been helpful in previous years? Questionable.
16. Would you consider the Vitamin C tablets modified your hay fever attacks? No.

Remarks: for more than a year I have been taking daily doses of combined vitamins.

Name: R. B.

Occupation: Life Insurance Program Planning.

Case II

B. B.

171 Grafton St.

Brooklyn, N. Y.

Age 19

History

Sneezing about 1 year. At about age 10 or 11, had frequent colds. All year round, complains of post nasal drip. Sneezing started in July last year. Worse in rainy weather. No chest symptoms. No allergies in family. No history of food allergies.

Examination

Mucosa —Hyperplastic.

Tonsils —Removed.

Turbinate—Inferior turbinate hypertrophied.

Discharge —Mucoid discharge both middle meati, more pronounced on right.

Therapy

6/13/44—Sneezing for past 2 weeks.

Allergy testing 4+ to ragweed, timothy.

7/4/44 —Started C.B. Pills, 1 T.I.D.

8/24/44—Increased to 2 T.I.D. 1944 pollen count 75

Occasional heart

burn. Nose not run-

ning. Generally better. 1943 pollen count 110

9/11/44—P.H. 7—C.B. Pills, 3 T.I.D.

Generally better.

Went without tablets

one day and had run-

ning nose. Immediately after taking 2

tablets, nose stopped 1944 pollen count 43

running. 1943 pollen count 56

Clinical Summary

6/13/44—Nasal mucosa acutely engorged; nasal ventilation markedly diminished; thin serous discharge.

7/1/44 —Findings similar to previous examination.

8/24/44—Nasal mucosa hyperplastic, but not engorged; slight mucoid discharge; nasal ventilation fair.

9/11/44—Nasal mucosa hyperplastic, but not congested; very little discharge; good nasal ventilation.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever?
First season.
2. Do you have food allergies as well? Yes.
3. Do you have asthmatic attacks during the hay fever season? No.
4. When did you start taking the Special C tablets?
July.
5. When did you first have any hay fever symptoms?
From end of May through summer.
6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less
 than previous years? (First season.)
7. How many tablets did you take at the beginning?
3 a day subsequently 6, then increased to 9 a day.

8. Did increasing the dosage give

- a. same
- b. better X
- results?

9. Do you think the Special Vitamin C tablets were

- a. no help
- b. helpful X

10. Did the tablets cause any irritation of the stomach? Slight heart burn.

11. Was there any increase in urination after taking tablets aside from hay fever symptoms? No.

12. Did you feel generally

- a. same
- b. worse
- c. better

than previous years? First season.

13. Did you also receive hay fever injections? No.

14. Have hay fever injections been helpful in previous years?

15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Remarks: Went without pills one day and had running nose again. Took only two tablets in the evening.

Name: Miss B. B.

Occupation: Student,

S. C.

6822 Fleet Street

Forest Hills, N. Y.

Age 51

History

cc: Has ragweed sensitivity for last 20 years. Otherwise has no complaints.

Hives occasionally.

Examination

Nasal Mucosa —Hyperplastic.

Septum —Deflected to right.

Inferior Turbinate—Hypertrophied.

Tonsils —Removed.

Drums —Retracted and thick.

Therapy

8/3/44 —Allergy testing.

High allergic to foods; also dust, feathers, Ragweed and Timothy. 1944 pollen count—rain

Given adrenalin to control hives due to the testing. 1943 pollen count 2

Started C.B. Pills, 1 T.I.D.

8/17/44—Complains of hives around the eyes, due,

patient states, to the C.B. pills. Also complaining of slight irritation of the stomach.

1944 pollen count 7*
1943 pollen count 37

8/31/44—Patient called by phone to state that she is having very little sneezing and is

feeling improved, more so than at any other year. No in-

crease in dosage 1944 pollen count 131
given. 1943 pollen count 236
*incomplete count due to showers.

Clinical Summary

- 8/3/44 —Nasal mucosa engorged; fairly profuse rhinorrhea.
8/17/44—There is angio-neurotic edema of both upper and lower lids; nasal mucosa not engorged and there is no rhinorrhea.
9/3/44 —Patient reported by telephone recurrence of hives, discontinued treatment herself.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

- For how many seasons have you had hay fever? 12 years.
- Do you have food allergies as well?
- Do you have asthmatic attacks during the hay fever season?
- When did you start taking the Special Vitamin C tablets? This year, by your advice.
- When did you first have any hay fever symptoms? Aug. 20, 1944.
- Would you consider your attacks than previous years?
 - worse
 - same
 - less
 Treatment discontinued.
- How many tablets did you take at the beginning? 3 a day.
- Did increasing the dosage give results?
 - same
 - better
 It gave me hives around the eyes.
- Do you think the Special Vitamin C tablets were
 - no help
 - helpful
 Very little help in sneezing.
- Did the tablets cause any irritation of the stomach? I presume so.
- Was there any increase in urination after taking tablets aside from hay fever symptoms? Yes
- Did you feel generally
 - same Almost the same
 - worse
 - better
 than previous years?
- Did you also receive hay fever injections? No.
- Have hay fever injections been helpful in previous years? No.
- Would you consider the Vitamin C tablets modified your hay fever attacks? Very little.

Remarks: Treatment discontinued because of hives.

Name: Mrs. S. C.

Occupation: Housewife.

G. P. C.

201 Crown Street

Brooklyn, New York

Age 35

History

Post nasal drip with right nasal discharge, chiefly greenish with odor. Duration 3 years. Onset with past

bladder trouble. Had ulcer in rectum. Had polyps removed. Had asthmatic attack in Florida. Was allergic to feathers and eggs in childhood. Found allergic to dust and ozite. X-rays show infection of right antrum. Has headache on right side. Has chills and fever with mucous in stools with foul odor. Occasional vertigo. No ear complaints. No sore throat. Pain in knees and elbows with sensation of stiffness in muscles and tiredness in back of head. Feels achy in feet. Generally tired. Typhoid, measles and mumps in childhood.

Examination

Mucosa	—Hyperplastic.
Discharge	—Muco-purulent discharge in right middle meatus. Both middle meatus open, left middle meatus shows muco-purulent discharge.
Septum	—Shows moderate spur posteriorly on right side.
Turbinates	—Hypertrophy of posterior tip or inferior turbinates.
Buccal Mucosa	—Normal.
Gingiva	—Shows low grade irritation.
Teeth	—Calcium deficiency.
Tongue	—Papillae slightly hypertrophied; posterior portion appears coated. Mucosa surface slightly hypertrophic.
Tonsils	—Removed. Extensive scarring of both anterior pillars; uvula has been removed.
Glands	—Enlarged, more pronounced on left side.
Epiglottis	—Lymphoid tissue at base of tongue.
Aryt.	—Muco-purulent discharge adherent to vocal chords.
Larynx	—Otherwise negative.

Therapy

11/8/43—Examination with allergy testing

Milk 1+	Cocoa 1+
Eggs 1+	Feathers 4+
Dust 4+	Ragweed 1+

11/15/43—Right antrum washed with 4+ returns.

12/20/43—Right antrum washed with 4+ returns.

12/27/43—Headache lessened.

2/4/44 —Right antrotomy at office.

2/14/44 —Normal recovery.

4/16/44 —Asthmatic condition has improved even with change of weather.

5/1/44 —Asthmatic condition continuing.

5/4/44 —Right antrum washed with zephrian 4+ old pus.

5/15/44 —Started on C.B. pills, 1 T.I.D.

6/1/44 —Attacks lessened.

6/15/44 —Asthmatic attacks stopped entirely.

7/2/44 —No asthmatic attacks since taking C.B. pills.

8/1/44 —No attacks during 1944 pollen count 0 the summer months. 1943 pollen count 0

Clinical Summary

5/15/44—Nasal mucosa congested; thin serous discharge, indicative of dust reaction.

- 6/1/44 — Nasal condition improved; post nasal discharge diminished.
 6/15/44 — Nasal fossae shows good ventilation space; very little congestion; only slight mucoid post nasal discharge.
 7/2/44 — Nasal breathing excellent; mucous membrane not engorged, slight post nasal discharge.
 8/1/44 — Nasal space good; mucosa appears fairly normal; slight mucoid discharge.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? No hay fever.
2. Do you have food allergies as well? Yes.
3. Do you have asthmatic attacks during the hay fever season? Yes.
4. When did you start taking the Special Vitamin C tablets? Off and on with other injections.
5. When did you first have any hay fever symptoms? Not sure.
6. Would you consider your attacks
 - a. worse
 - b. same Asthma attacks stopped.
 - c. less X
 than previous years?
7. How many tablets did you take at the beginning? 1 a day.
8. Did increasing the dosage give
 - a. same
 - b. better Can't judge.
 results?
9. Do you think the Special Vitamin C tablets were
 - a. no help *
 - b. helpful X
10. Did the tablets cause any irritation of the stomach? None.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? None.
12. Did you feel generally
 - a. same
 - b. worse
 - c. better X
 than previous years.
13. Did you also receive hay fever injections? I received calcium and histidine.
14. Have hay fever injections been helpful in previous years? No.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Remarks: I have had a bad sinus infection. Dr. Ruskin operated on me in February, and I have had a series of injections after, until June.

Case V

Name: G. P. C.

Occupation: Housewife.

J. C.

39 W. 55 St.

New York, N. Y.

Age 22

History

Post nasal drip for last 8-10 years. Nasal obstruction, chiefly at night, alternating, worse in rainy weather. Has swelling of tissues of forehead. Headaches with nasal obstruction. Heaviness in head. Had steady headache for 19 days recently. Has hay fever in August and also has asthmatic condition. An uncle died of asthma. No hives. No eczema. Stuffiness in ears at times.

Operations: D & C 1½ years ago, Broncho-pneumonia 4-5 years ago.

Examination

Mucosa	—Engorged, nasal fossae very much obstructed.
Discharge	—Sero-mucoid discharge in both middle meati.
Septum	—In mid position.
Transillumination	—Moderately diminished on both sides.
Tonsils	—Removed.

Therapy

7/27/44 — Examination—allergic testing:

Dust	4+	Chocolate	4+
Milk	4+	Feathers	4+
Eggwhite	4+	Timothy	4+
		Ragweed	4+

8/3/44 — Started C. B. Pills, 1 T.I.D. 1944 pollen count— rain

Started hay fever int. 1943 pollen count 2

8/15/44 — Starting first symptoms of hay fever. C.B. Pills, 2 T.I.D.; slight increase in urination. 1944 pollen count 32
1943 pollen count 25

9/5/44 — Sneezing less than in previous years. C.B. Pills, 3 T.I.D. 1944 pollen count 319
No tearing. 1943 pollen count 61

9/15/44 — No sneezing. 1944 pollen count 75
1943 pollen count 51

9/20/44 — No symptoms for the remainder of the sea-season. 1944 pollen count 10
1943 pollen count 48

Clinical Summary

8/15/44 — Nasal mucosa engorged; nasal fossae markedly obstructed; mucoid discharge.

9/5/44 — Nasal mucosa moderately congested; nasal fossae shows fair breathing space; moderate mucoid discharge.

9/15/44 — Nasal fossae fairly clear; mucosa not congested; mucoid discharge slight; patient appears quite comfortable.

9/20/44 — Good nasal space; mucosa not engorged; very little nasal discharge.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 8 years.

2. Do you have food allergies as well? Yes.
3. Do you have asthmatic attacks during the hay fever season? Yes.
4. When did you start taking the Special Vitamin C tablets? Beginning of August.
5. When did you first have any hay fever symptoms? Middle of August.
6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less X
 than previous years?
7. How many tablets did you take at the beginning? 3 a day.
8. Did increasing the dosage give
 - a. same
 - b. better X
 results?
9. Do you think the Special Vitamin C tablets were
 - a. no help
 - b. helpful X
10. Did the tablets cause any irritation of the stomach? No.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? Possible.
12. Did you feel generally
 - a. same
 - b. worse
 - c. better X
 than previous years?
13. Did you also receive hay fever injections? Yes.
14. Have hay fever injections been helpful in previous years?
This is the first season I have had the injections.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Name: J. C.

Occupation: Actress.

Case VI

S. D.

Cedar Island

Larchmont, N. Y. Age 44

History

6-8-42 For the last 4 weeks has had nasal stuffiness and some sneezing, moderate. Has taken neosynephrine. Slight post nasal discharge. No sore throat. No hay fever or asthma. Had cardiac attack 3 years ago.

Examination

Mucosa	—Congested
Discharge	—Muco-purulent discharge both middle meati.
Septum	—Deflected to right and left
Turbinates	—Inferior hypertrophied. Both middle meatus partly obstructed
Buccal Mucosa	—Normal
Post Rhinoscopy	—Gingiva in fair condition
Tongue	—Moderately coated
Tonsils	—Diseased
Larynx	—Negative
Drum	—Slightly retracted, otherwise negative

Therapy

- Examination with allergy testing. Allergic to most of foods with 3+ to Ragweed and Timothy.
- 4-20-44—Started injections for Spring grasses.
- 6-15-44—Started hay fever injections with C.B. pills 1 T.I.D.
- 7-1-44—Increased dosage to 2 T.I.D. feeling better than in previous seasons.
- 7-24-44—Very few symptoms of hay fever.
- 8-1-44—Better this season than during any of the other seasons. 1944 pollen count 0
1943 pollen count 0

Clinical Summary

- 6-15-44—Nasal mucosa moderately engorged; moderate sero-mucoid discharge; moderate post nasal discharge
- 7-1-44—Nasal fossae fairly clear; only slight mucosal engorgement; very little nasal discharge
- 7-24-44—Nasal fossae clear; no post nasal discharge
- 8-1-44—Nasal fossae clear; mucosa not congested; no serious discharge

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 3.
2. Do you have food allergies as well? No.
3. Do you have asthmatic attacks during the hay fever season? No.
4. When did you start taking the Special Vitamin C tablets? Last year.
5. When did you first have any hay fever symptoms? 3 years ago.
6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less X
 than previous years?
7. How many tablets did you take at the beginning? 3 a day.
8. Did increasing the dosage give
 - a. same
 - b. better
 results?
9. Do you think the Special Vitamin C Tablets were
 - a. no help
 - b. helpful X
10. Did the tablets cause any irritation of the stomach? Slight indigestion.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? No.
12. Did you feel generally
 - a. same
 - b. worse
 - c. better X
 than previous years?
13. Did you also receive hay fever injections? Yes.
14. Have hay fever injections been helpful in previous years? Yes.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Name: S. D.
Occupation: Motion Picture Distributor.

R. F.
385 Central Park W.
New York, New York. Age 31.

History

Hay fever for past ten years, worse for past two years. No food allergies.

Examination

Mucosa —Moderately hyperplastic.
Septum —Deflected to right.
Turbinates —Inferior turbinates hypertrophied.
Tonsils —Removed.
Transillumination—Diminished illumination both sides.

Therapy

6-4-44—Started C.B. Pills 3 T.I.D.

Patient did not return to the office for any treatment but reported by phone and letter that the C.B. Pills seemed to lessen the severity of his attacks. No increase in urine or irritation of the stomach. The same dosage taken throughout the season.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? Badly, for the last two.
2. Do you have food allergies as well? No.
3. Do you have asthmatic attacks during the hay fever season? No.
4. When did you start taking the Special Vitamin C tablets? June, 1944.
5. When did you first have any hay fever symptoms? May.
6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less
 than previous years?
7. How many tablets did you take at the beginning? 3 a day.
8. Did increasing the dosage give
 - a. same
 - b. better
 results? Did not increase.
9. Do you think the Special Vitamin C Tablets were
 - a. no help
 - b. helpful Slightly.
10. Did the tablets cause any irritation of the stomach? No.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? No.
12. Did you feel generally
 - a. same
 - b. worse
 - c. better Slightly.
 than previous years?
13. Did you also receive hay fever injections? Yes.

14. Have hay fever injections been helpful in previous years? Slightly.
 15. Would you consider the Vitamin C tablets modified your hay fever attacks? Slightly.
- Remarks: Hay fever attacks vary so widely from day to day that to correlate the effect of the vitamin "C" with the physical condition is difficult. It was not a complete cure.

Name: R. F.

Occupation: Engineer.

B. G.
73 Avenue
Flushing, L. I. Age 28

History

Hay fever for two seasons. No food allergies but slight asthmatic attacks during the season.

Examination

Mucosa —Hyperplastic and thickened.
Septum —Moderately deflected.
Turbinates—Inferior turbinates hypertrophied.
Tonsils —Diseased.

Therapy

9-24-44—Started C.B. pills 3 T.I.D.

Patient did not return to office but reported by letter that he feels better this year even though he started the C.B. pills in the middle of the season. States of no irritation to the stomach or of bladder disturbances. Did not take hay fever injections with the C.B. pills.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 2.
2. Do you have food allergies as well? No.
3. Do you have asthmatic attacks during the hay fever season? Slight.
4. When did you start taking Special Vitamin C tablets? September.
5. When did you first have any hay fever symptoms? 2 years ago.
6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less
 than previous years?
7. How many tablets did you take at the beginning? 9 a day.
8. Did increasing the dosage give
 - a. same
 - b. better
 results?

9. Do you think the Special Vitamin C Tablets were
 - a. no help
 - b. helpful X
10. Did the tablets cause any irritation of the stomach? No.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? No.
12. Did you feel generally
 - a. same X
 - b. worse
 - c. better
 than previous years?
13. Did you also receive hay fever injections? No.
14. Have hay fever injections been helpful in previous years? No.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Remarks: I definitely believe that the tablets were helpful.

Name: B. G.

Occupation: Salesman.

M. H. (Patient is Dr. Ruskin's Bank Teller)

History

Hay fever for the past 35 years.

No food allergies.

No asthmatic attacks.

Examination

No physical examination.

Therapy

9-1-44 —C.B. pills 3 T.I.D. 1944 pollen count 106
 Patient did not return 1943 pollen count 235
 to office but reported by phone.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 35 years.
2. Do you have food allergies as well? No.
3. Do you have asthmatic attacks during the hay fever season? No.
4. When did you start taking the Special Vitamin C tablets? Sept. 1, 1944.
5. When did you first have any hay fever symptoms? 35 years ago.
6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less X
 than previous years?
7. How many tablets did you take at the beginning? 9 a day.
8. Did increasing the dosage give
 - a. same
 - b. better X
 results?
9. Do you think the Special Vitamin C Tablets were
 - a. no help
 - b. helpful

10. Did the tablets cause any irritation of the stomach? No.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms?
12. Did you feel generally
 - a. same
 - b. worse
 - c. better X
 than previous years?
13. Did you also receive hay fever injections? Not this year.
14. Have hay fever injections been helpful in previous years? Yes.
15. Would you consider the Vitamin C tablets modified your hay fever attack? Yes.

Remarks: I started taking the tablets late in the season.

Name: M. H.

Occupation: Bank Teller.

N. H.

1307 Sixth Ave.

New York, N. Y. Age 29

History

Has had some trouble for 4 years. Hay fever last summer complicated with asthma and pleurisy. Had a cold with laryngitis a few weeks ago. Had allergy tests 3 years ago. Sensitive to dust.

Appendectomy in March 1944.

Allergic—Acne. Receiving X-ray therapy.

Examination

Pupils react to light and accommodation.

Mucosa	—Hyperplastic
Discharge	—Mucoid nasal discharge in right middle meatus
Septum	—Deflected to right with partial obstruction. Inferior turbinates moderately hypertrophied.
Transillumination	—Both antra and right frontal diminished illumination.
Buccal Mucosa	—Slightly thickened.
Teeth	—Calcium deficiency.
Tonsils	—Removed. Small rest on left side.
Pharynx	—Shows lymphoid hyperplasia
Glands	—Ant. cerv. glands markedly hypertrophied and enlarged, posterior glands enlarged and palpable.
Larynx	—Negative.

Right Ear Drum —Thickened and retracted. Posterior $\frac{1}{2}$ opaque.

Left Ear Drum —Thickened and retracted.

Therapy

8-1-44 —Examination and Allergy testing
 Dust 3+ Milk —
 Feathers 2+ Egg —
 Chocolate 1+ Timothy 3+
 Ragweed 4+

1944 pollen count 0

1943 pollen count 0

8-3-44	—Started dust and resp. injections, started C. B. pills 3 T.I.D.	1944 pollen count— rain
8-7-44	—Relieved of some asthmatic attacks with C. B. pills.	1943 pollen count 2
8-11-44	—Relieved by taking 3 tablets when asthmatic attack is more severe. No irritation of stomach or bladder.	1944 pollen count 7 1943 pollen count 6
		1944 pollen count 26 1943 pollen count 27

Clinical Summary

8-3-44 —Nasal mucosa acutely congested; nasal fossae obstructed; moderately profuse sero-mucinous discharge.

8-7-44 —Nasal mucosa less congested; moderate nasal breathing space; nasal discharge slight.

8-11-44 —Nasal fossae clear; very little mucosal congestion; good breathing space; slight nasal discharge.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? Two.
2. Do you have food allergies as well? Yes.
3. Do you have asthmatic attacks during the hay fever season? First year.
4. When did you start taking the Special Vitamin C tablets? Beginning 2nd year attacks.
5. When did you first have any hay fever symptoms? 2 years ago.
6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less
 than previous years?
7. How many tablets did you take at the beginning? 6 daily increasing to 9 daily—total of 270.
8. Did increasing the dosage give
 - a. same
 - b. better results?
9. Do you think the Special Vitamin C Tablets were
 - a. no help
 - b. helpful
10. Did the tablets cause any irritation of the stomach? No.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? No.
12. Did you feel generally
 - a. worse
 - b. same
 - c. better
 than previous years?
13. Did you also receive hay fever injections? No.
14. Have hay fever injections been helpful in previous years? Never had any.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Remarks: Had dust injections.

Name: N. H.

Occupation: Dancer.

Case X

E. C. H.

7200 Ridge Blvd.

Brooklyn, N. Y. Age 65

History

1-19-43—Had a cold in December, but has been sneezing for some time before that. Then noticed left nostril obstruction; now both are obstructed. Eyes feel tired and heavy, slight headache in mornings.

Examination

Mucosa —Hyperplastic.
Mucoid discharge both sides, mucosa engorged obstructing both nasal fossae.

Buccal mucosa—Normal.

Teeth —Well calcified.

Tongue —Smooth.

Tonsils —Small, deeply buried and congested.

Larynx —Congested.

Ears —Both, thickened and retracted.

Therapy

8-28-44—C.B. Pills, 3 T.I.D. 1944 pollen count 56*
1943 pollen count 98

9-10-44—Relieved of sneezing by C.B. Pills. No increase of urination. Patient states she believes they help elimination. 1944 pollen count 50
1943 pollen count 32

9-20-44—No sneezing during entire season. 1944 pollen count 10
1943 pollen count 48

*incomplete count due to showers.

Clinical Summary

8-28-44—Nasal fossae completely closed; mucosa is engorged; thin serous discharge; profuse, slight eczema of both nasal alae.

9-10-44—Nasal mucosa moderately congested; patient has fair breathing space; slight mucoid discharge.

9-20-44—Nasal fossae clear; mucoid discharge diminished; very little nasal congestion.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? This is the first.
2. Do you have food allergies as well? Yes.
3. Do you have asthmatic attacks during the hay fever season? Some.
4. When did you start taking the Special Vitamin C tablets? Aug. 28th.
5. When did you first have any hay fever symptoms? This year.

6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less X
 than previous years?
7. How many tablets did you take at the beginning? 3 tablets 3 times a day continuously.
8. Did increasing the dosage give
 - a. same I have a feeling they helped
 - b. better elimination a better formed stool results?
9. Do you think the Special Vitamin C Tablets were
 - a. no help
 - b. helpful X
10. Did the tablets cause any irritation of the stomach? Not that I am aware of.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? No.
12. Did you feel generally
 - a. same
 - b. worse
 - c. better X
 than previous years?
13. Did you also receive hay fever injections? No.
14. Have hay fever injections been helpful in previous years?
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Name: E. C. H.

Occupation: Clerical Work.

Case XI

E. H.

142-02 Franklin Ave,
Flushing, New York. Age 45*History*

cc: Has had hay fever for last 16 years, sneezing, rhinitis, nasal obstruction. Onset around August 28th, lasts one month.

Examination

Mucosa	—Very much thickened and hyperplastic.
Turbinates	—Both inferior and middle turbinates hypertrophied.
Septum	—Moderately deflected high to the right and low to the left.
Tonsils	—Removed.
Transillumination	—Diminished both maxillary and frontals.

Therapy

- 5-19-44—Started C.V. Pills 1 T.I.D.
 7-2-44—No irritation of stomach. Increase in urination at night.
 8-24-44—No increase in dosage.
 Patient feeling better, very little sneezing.
 9-30-44—Patient states he was more comfortable during the hay fever season than at any other
- 1944 pollen count 75
 1943 pollen count 110

period. Very little 1944 pollen count 7 sneezing during the 1943 pollen count—rain four weeks.

Clinical Summary

- 7-2-44—Nasal mucosa engorged, moderately, moderate mucous serous discharge; nasal ventilation poor.
- 8-24-44—Nasal mucosa hyperplastic, but not engorged; slight mucoid discharge; nasal ventilation fair.
- 9-30-44—Nasal mucosa not congested; nasal ventilation good; very little mucoid discharge.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 12 seasons.
 2. Do you have food allergies as well? Oat, cabbage.
 3. Do you have asthmatic attacks during the hay fever season? No.
 4. When did you start taking the Special Vitamin C tablets? May 1944.
 5. When did you first have any hay fever symptoms? Sept. 2.
 6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less X
 than previous years?
 7. How many tablets did you take at the beginning? 3 a day.
 8. Did increasing the dosage give
 - a. same
 - b. better X
 than previous years?
 9. How many tablets did you take at the beginning? 3 a day.
 10. Did increasing the dosage give
 - a. same
 - b. better X
 results?
 11. Do you think the Special Vitamin C tablets were
 - a. no help
 - b. helpful X
 12. Did the tablets cause any irritation of the stomach? No.
 13. Was there any increase in urination after taking tablets aside from hay fever symptoms? During the night only.
 14. Did you feel generally
 - a. same
 - b. worse
 - c. better X
 than previous years?
 15. Did you also receive hay fever injections?
 16. Have hay fever injections been helpful in previous years? No.
 17. Would you consider the Vitamin C tablets modified your hay fever attacks? Definitely.
- Remarks: I was much more comfortable during the

past hay fever period and also had better after effects.

Name: E. H.

Occupation: Salesman.

E. L.

187 Pinelhurst Ave.

New York, N. Y. Age 11½

History

Hay fever for 4 years. Some food allergies.
No asthmatic attacks.

Examination

Mucosa — Congested.

Turbinates—Inferior. turbinates occlude both nasal fossae.

Discharge — Profuse serous discharge.

Septum — Nasal septum in midline.

Tonsils — Removed.

Therapy

7-6-44 — Started C.B. pills 1 T.I.D.

First hay fever symptoms in June.

Patient did not return to office, but mother reported by phone that the patient has been greatly benefitted by the C.B. pills. No increase in dosage. No irritation of bladder or stomach.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 4.
2. Do you have food allergies as well? Yes.
3. Do you have asthmatic attacks during the hay fever season? No.
4. When did you start taking the Special Vitamin C tablets? July.
5. When did you first have any hay fever symptoms? June.
6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less than previous years?
7. How many tablets did you take at the beginning? 3 a day.
8. Did increasing the dosage give
 - a. same
 - b. better results?
9. Do you think the Special Vitamin C tablets were
 - a. no help
 - b. helpful
10. Did the tablets cause any irritation of the stomach? No.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? No.
12. Did you feel generally
 - a. same
 - b. worse
 - c. better than previous years?

13. Did you also receive hay fever injections? No.
14. Have hay fever injections been helpful in previous years? Yes.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Name: E. L.

Occupation: Schoolboy. 11½ years old

W. L.

15 E. 36 St.

New York, N. Y. Age 46

History

cc: Hay fever for 30 years with asthmatic attacks.

Examination

Nasal mucosa hyperplastic, septum markedly deflected to right. Bilateral maxillary and ethmoidal sinusitis. Hypertrophic inferior turbinates.

Profuse sero-mucous discharge.

Therapy

6/1/44 — Started C.B. Pills, 1 T.I.D.

6/9/44 — No sneezing since taking pills, no itching. Started hay fever injections.

7/5/44 — Slight increase in urination. Increased to 2 T.I.D.

8/1/44 — No sneezing. General condition improved. 1944 pollen count 0 Increased to 3 T.I.D. 1943 pollen count 0

8/30/44 — No sneezing. No asthmatic attacks. H.P. 615. 1944 pollen count 161 1943 pollen count 118

9/15/44 — General condition much better than in previous years. 1944 pollen count 75 1943 pollen count 51

Clinical Summary

6/9/44 — Nasal mucosa slightly congested; moderate nasal discharge; nasal fossae moderately obstructed.

7/5/44 — Nasal fossae moderately obstructed; slight mucoid discharge; mucosa slightly congested.

8/1/44 — Nasal mucosa not engorged, nasal fossae fairly clear; slight mucoid discharge.

8/30/44 — Nasal mucosa not congested; nasal fossae clear; slight mucoid discharge.

9/15/44 — Nasal mucosa not congested; nasal fossae quite clear; slight mucoid discharge.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 30 years.
2. Do you have food allergies as well? No.
3. Do you have asthmatic attacks during the hay fever season? Yes.
4. When did you start taking the Special Vitamin C tablets? June 1, 1944.
5. When did you first have any hay fever symptoms? August 20, 1944.

6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less X considering the bad weather than previous years?
7. How many tablets did you take at the beginning? 3 a day.
8. Did increasing the dosage give
 - a. same
 - b. better X results?
9. Do you think the Special Vitamin C tablets were
 - a. no help
 - b. helpful X
10. Did the tablets cause any irritation of the stomach? No.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? Yes.
12. Did you feel generally
 - a. same
 - b. worse
 - c. better X than previous years?
13. Did you also receive hay fever injections? Yes.
14. Have hay fever injections been helpful in previous years? Yes.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Decidedly.

Remarks: Better general condition.

Name: W. C.

Occupation: Radio Director.

M. M.

215 S. 5th Avenue

New Brunswick, N. J.

History

1935—Frontal pains around eyes radiating to occipitals. At times pains in both cheeks. After nasal operation 6 years ago, developed hay fever, occasional nasal drip, vertigo and neuritis. Occasional pain in ears.

Teeth—Normal.

Tonsils—Diseased.

Bilateral pain sinusitis—polypoid, left antrum 2+

Septum—Shows large post-operative perforation, nasal fossae obstructed.

Therapy

9/1/44—Started C.B. pills, 1 T.I.D. Started hay fever symptoms August 14th.

9/20/44—Some irritation of stomach. Some increase in urination.

10/1/44—Feeling better this year than previously even with starting the tablets after the symptoms had started. Also did not take the tablets regularly.

1944 pollen count	106
1943 pollen count	235

1944 pollen count	10
1943 pollen count	48

1944 pollen count	3
1943 pollen count	2*

*incomplete count due to showers.

Clinical Summary

9/20/44—Nasal mucosa less congested than at any previous examination; respiratory space fair; post nasal mucoid discharge, slight.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 15 years.
 2. Do you have food allergies as well? No.
 3. Do you have asthmatic attacks during the hay fever season? No.
 4. When did you start taking the Special Vitamin C tablets? Sept. 1, 1944.
 5. When did you first have any hay fever symptoms? Aug. 14, 1944.
 6. Would you consider your attacks
 - a. worse
 - b. same
 - c. better X than previous years?
 7. How many tablets did you take at the beginning? 3 a day.
 8. Did increasing the dosage give
 - a. same No increase
 - b. better results?
 9. Do you think the Special Vitamin C tablets were
 - a. no help A little.
 - b. helpful
 10. Did the tablets cause any irritation of the stomach? Yes.
 11. Was there any increase in urination after taking tablets aside from hay fever symptoms? Yes.
 12. Did you feel generally
 - a. same
 - b. worse
 - c. better X than previous years?
 13. Did you also receive hay fever injections? No.
 14. Have hay fever injections been helpful in previous years? No.
 15. Would you consider the Vitamin C tablets modified your hay fever attacks? A little.
- Remarks: I was at the White Mts. for 3 weeks and had a few light attacks in the morning, but have had 2 bad attacks since returning.
- Name: M. M.
- Occupation: Salesman.
- J. M.
73 Avenue
Flushing, L. I. Age 35
- History*
- Hay fever for about 24 years. No food allergies, but asthmatic attacks with hay fever symptoms.
- Nasal Examination*
- Negative.

Therapy

1/1/44—Started C.B. pills, 1 T.I.D. First hay fever 1944 pollen count 106 symptoms Aug. 15th. 1943 pollen count 235

Patient did not return to office but reported by phone that she has felt much better this season than in any previous season. Increased dosage from 1 to 2 T.I.D. Increasing dosage seems to be more helpful, but caused some gastric upset for a few days; also an increase in urine.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 1921.
2. Do you have food allergies as well? No.
3. Do you have asthmatic attacks during the hay fever season? Yes.
4. When did you start taking the Special Vitamin C tablets?
5. When did you first have any hay fever symptoms? Aug. 15.
6. Would you consider your attacks
 - a. worse X
 - b. same
 - c. less
 than previous years?
7. How many tablets did you take at the beginning? 3.
8. Did increasing the dosage give
 - a. same
 - b. better X
 results?
9. Do you think the Special Vitamin C tablets were
 - a. no help
 - b. helpful X
10. Did the tablets cause any irritation of the stomach? A little upset first few days.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? Yes.
12. Did you feel generally
 - a. same
 - b. worse
 than previous years?
13. Did you also receive hay fever injections? Some years ago, 1937.
14. Have hay fever injections been helpful in previous years? No.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Name J. M.

Occupation: Housewife.

Case XVI

G. E. P.

935 St. Nicholas Avenue

New York, New York Age 38

History

5/1/44—Nasal obstruction and discharge with sneezing and rhinitis since November and December. Headaches at times. Has used vaso constrictor. Tickling in throat. No ear com-

plaints except stuffiness. Has wheezing in chest. No family history of hay fever or asthma. All other negative.

Examination

Mucosa	—Hyperplastic, engorged, allergic in type.
Septum	—In mid position.
Turbinates	—Polypoid changes in right middle turbinate.
Throat	—Buccal mucosa normal.
Tonsils	—Removed.
Pharynx	—Negative.
Larynx	—Negative.
Drum	—Show slight retraction.

Therapy

5/1/44—Examination—Allergy testing

milk	+	feathers	1+
eggs	3+	dust	4+
chocolate	2+	timothy	1+
ragweed 1+			

5/3/44—Started injections concentrated dust and respiratory UBA.

7/24/44—Sub mucous resection at office.

8/1/44—C.B. pills, started 2 1944 pollen count 0
T.I.D. 1943 pollen count 0

8/11/44—H.P. 7.0. 1944 pollen count 26
 1943 pollen count 27

8/24/44—C.B. pills, started 3 1944 pollen count 110
T.I.D. 1943 pollen count 110

9/4/44—States of slight irritation of stomach.
Otherwise less sneezing than in previous years. 1944 pollen count 238
 1943 pollen count 45

10/1/44—No sneezing. Better than in previous years 1944 pollen count 3
 1943 pollen count 2*
*incomplete count due to showers

Clinical Summary

8/11/44—Both inferior turbinates engorged; partial nasal obstruction; mucoid nasal discharge.

8/24/44—Inferior turbinates less congested; fair amount of nasal space; diminished mucoid discharge.

10/1/44—Nasal mucosa appears quite normal; excellent nasal space; inferior turbinates appear normal; nasal discharge within normal range.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 2 years.
2. Do you have food allergies as well? Yes.
3. Do you have asthmatic attacks during the hay fever season? Slight year round.
4. When did you start taking the Special Vitamin C tablets? August.
5. When did you first have any hay fever symptoms? All year.

6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less X
 than previous years?
7. How many tablets did you take at the beginning?
6 daily then 9 daily.
8. Did increasing the dosage give
 - a. same
 - b. better X
 results?
9. Do you think the Special Vitamin C tablets were
 - a. no help
 - b. helpful X
10. Did the tablets cause any irritation of the stomach?
Slight.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? No.
12. Did you feel generally
 - a. same
 - b. worse
 - c. better X
 than previous years?
13. Did you also receive hay fever injections? No.
14. Have hay fever injections been helpful in previous years? Never had any.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Remarks: Improvement better over previous years, but I did not have medical treatment before for same.

Name: G. E. P.

Occupation: Trained Nurse.

Case XVII

R. R.

135-48 77th Ave.

Flushing, New York Age 6

History

Had hives at age of 3 with patches on chest but no nasal symptoms. At 4, developed sneezing and rhinitis in August and September. Has been treated and found sensitive to cauliflower, wheat, beef, grapes, strawberry, rice, spinach, pineapple, beets, lettuce, tomato, salmon, string beans, wool and dust. Not much hives now.

Operations—none. Mumps at 18 months.

Hereditary—Father gets occasional hives.

Examination

Sinuses—negative.

Therapy

6/17/44—Allergic testing

dust	4+	milk	4+
feathers	4+	egg white	4+
chocolate	4+	ragweed	4+

C.B. pills started T.I.D.

6/30/44—Patient appears the same.

7/1/44—C.B. pills stopped. Not much relieved. Taking nucleic acid powder instead with relief.

Clinical Summary

6/30/44—Nasal mucosa congested and engorged; slight amount mucoid discharge; nasal space fair.

7/1/44—Nasal mucosa engorged; slight mucoid discharge.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 2 years.
2. Do you have food allergies as well? Yes.
3. Do you have asthmatic attacks during the hay fever season? No.
4. When did you start taking the Special Vitamin C tablets? July, 1944.
5. When did you first have any hay fever symptoms? August.
6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less X
 than previous years?
7. How many tablets did you take at the beginning? 3 daily.
8. Did increasing the dosage give
 - a. same No increase.
 - b. better
 results?
9. Do you think the Special Vitamin C tablets were
 - a. no help X
 - b. helpful
10. Did the tablets cause any irritation of the stomach? No
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? No.
12. Did you feel generally
 - a. same
 - b. worse
 - c. better X
 than previous years?
13. Did you also receive hay fever injections? No.
14. Have hay fever injections been helpful in previous years? No.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? No.

Remarks: Vitamin C tablets stopped after 2 weeks. Now taking Nucleic Acid powder with relief.

Name: R. R.

Occupation: Child 6 years.

Case XVIII

S. R.

240 West 73rd Street

New York, N. Y. Old patient

History

P.C.—Had plastic four years ago. For last year he has had sneezing and running nose, but has had no relief. Occasional headache. Hay fever for 17 years. Asthmatic attacks occasionally in hay fever season.

Examination

Patient has had a nasal plastic with partial collapse of both nasal alae.

Mucosa—Hyperplastic and engorged.

Turbinates—Inferior turbinates hypertrophied.

Discharge—Serous nasal discharge; redness and excoriation of both nasal alae.

Therapy

4/14/44 —Allergy testing 4+ to dust and feathers.

4/19/44 —Series of Cane. Dust and Resp. Injections started.

6/2/44 —Started Vitamin C tablets, 1 T.I.D.

6/28/44 —Increased to 2 T.I.D.

7/1/44 —Increased to 3 T.I.D.

8/7/44 —Sneezing decreased.

Feeling of digestive disturbances. Increased diaphoresis.

1944 pollen count 4
1943 pollen count 6

8/28/44 —Slight increase of urine, otherwise less sneezing than previously.

1944 pollen count 56*
1943 pollen count 98

9/21/44]—Did not take the Vitamin C during this period and sneezed more than at the time

9/28/44]—she was taking them.

* Incomplete due to showers.

Clinical Summary

6/2/44 —Nasal mucosa markedly congested; very little nasal space; serous nasal discharge.

6/28/44—Moderate nasal congestion; nasal fossae show fair degree of space; slight mucoid discharge.

8/7/44 —Nasal mucosa slightly congested; good nasal space; slight mucoid discharge.

8/28/44—Good nasal passageway; mucosa appears fairly normal; slight mucoid discharge.

9/21/44—Good nasal space; nasal mucosa appears fairly normal.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever?
17.
2. Do you have food allergies as well? Yes.
3. Do you have asthmatic attacks during the hay fever season? Occasionally.
4. When did you start taking the Special Vitamin C tablets? June, 1944.
5. When did you first have any hay fever symptoms? Aug. 18, 1944.
6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less X
 than previous years?
7. How many tablets did you take at the beginning? 3 a day., subsequently 9 a day—altogether 400 tablets.
8. Did increasing the dosage give
 - a. same
 - b. better X
 results?
9. Do you think the Special Vitamin C tablets were
 - a. no help
 - b. helpful X

10. Did the tablets cause any irritation of the stomach? Once in a while.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? Yes.
12. Did you feel generally
 - a. same
 - b. worse
 - c. better X
 than previous years?

13. Did you also receive hay fever injections? Yes.

14. Have hay fever injections been helpful in previous years? Yes.

15. Would you consider the Vitamin C tablets modified your hay fever attacks. Yes.

Remarks: Did not take the pills from Sept. 21st to Sept. 28th and missed them and sneezed during that period.

Name: S. H. Occupation: Saleslady.

A. R.

532 W. 143rd Street

New York, N. Y.

History

About five years ago had nasal obstruction. Occasional headache. Last August had hay fever. Frontal headaches. Eyes feel heavy, feel tired. Has trouble with menses. History of hay fever for thirteen years. No allergies to food.

Examination

Mucosa—Vasomotor rhinitis.

Septum—Moderately deflected.

Impacted middle turbinate.

Bilateral hyperplastic ethmoiditis.

Therapy

Turbinectomy in 1933

7/15/44—Started on C.B. pills, 1 T.I.D.

8/1/44 —Slight increase of urination. No irritation of stomach.

1944 pollen count 0	1943 pollen count 0
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8/15/44—C.B. pills increased to 3 T.I.D.

1944 pollen count 32	1943 pollen count 25
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9/1/44—Increase in urination. Otherwise feeling fine with very little sneezing.

Clinical Summary

8/1/44 —Nasal mucosa slightly engorged; very little nasal discharge; moderate nasal obstruction.

8/15/44—Nasal fossae show good space; mucosa not engorged; very little nasal discharge.

9/1/44—Nasal mucosa hyperplastic, but shows no vasomotor disturbances; nasal fossae fairly clear; very little nasal discharge.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 13 years.
2. Do you have food allergies as well? No.
3. Do you have asthmatic attacks during the hay fever season? No.

4. When did you start taking the Special Vitamin C tablets? Middle of July.
5. When did you first have any hay fever symptoms? End of August.
6. Would you consider your attacks
 - a. worse
 - b. same X
 - c. less
 than previous years?
7. How many tablets did you take at the beginning? 3 a day.
8. Did increasing the dosage give
 - a. same
 - b. better X
 results?
9. Do you think the Special Vitamin C tablets were
 - a. no help
 - b. helpful X
10. Did the tablets cause any irritation of the stomach? No.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? Yes.
12. Did you feel generally
 - a. same
 - b. worse
 - c. better X
 than previous years?
13. Did you also receive hay fever injections? No.
14. Have hay fever injections been helpful in previous years? Never took any.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Remarks: Due to a bad season I was not as well as the past two years.

Name: J. C.

Occupation: Actress.

E. S.

Flushing, L. I. Age 40

History

Hay fever for past twenty years. No food allergies.

Examination

Vasomotor rhinitis.

Therapy

9/2/44—Started C.B. pills, 3

T.I.D. First hay

fever symptoms August 15th 1944 pollen count 346
1943 pollen count 233

Patient did not return to office for further treatment but reported by phone that she is feeling much better than she had in previous years while she was taking hay fever injections. None given this year. The C.B. pills seem to modify her attacks a great deal. No irritation of stomach or bladder reported.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? About 20.

2. Do you have food allergies as well? No.
 3. Do you have asthmatic attacks during the hay fever season? No.
 4. When did you start taking the Special Vitamin C tablets? Sept.
 5. When did you first have any hay fever symptoms? Aug. 15.
 6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less X
 than previous years?
 7. How many tablets did you take at the beginning? 9 a day.
 8. Did increasing the dosage give
 - a. same
 - b. better
 results?
 9. Do you think the Special Vitamin C tablets were
 - a. no help
 - b. helpful X
 10. Did the tablets cause any irritation of the stomach? No.
 11. Was there any increase in urination after taking tablets aside from hay fever symptoms? No.
 12. Did you feel generally
 - a. same
 - b. worse
 - c. better X
 than previous years?
 13. Did you also receive hay fever injections? Yes.
 14. Have hay fever injections been helpful in previous years? Yes.
 15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.
- Name: E. S.
Occupation: Housewife.
F. B. S.
2214 64th Street
Brooklyn, N. Y. Age 26
- History**
- Has had hay fever for last 4 years. About 2 weeks ago had nasal obstruction. Has nasal stuffiness, sneezing and running. Had 6 injections of hydrochloric acid for hay fever. Operations—Thyroidectomy 12 years ago.
- Examination**
- | | |
|-------------------|--|
| Septum | —Deflected sharply to the left. |
| Turbinates | —Inferior turbinates hypertrophied. |
| Mucosa | —Hyperplastic—nasal fossae markedly obstructed. |
| Discharge | —Mucoid discharge both middle meati—serous mucoid discharge. |
| Transillumination | —Moderately diminished both sides. |
| Tonsils | —Removed. |
- Therapy**
- 6/3/44 —Started hay fever injections.
Started C.B. Pills, 1 T.I.D.

Discharge—Serous nasal discharge; redness and excoriation of both nasal alae.

Therapy

4/14/44 —Allergy testing 4.5% to dust and feathers.
4/19/44 —Series of Cane, Dust and Resp. Injections started.

6/2/44 —Started Vitamin C tablets, 1 T.I.D.
6/28/44 —Increased to 2 T.I.D.

7/1/44 —Increased to 3 T.I.D.

8/7/44 —Sneezing decreased.
Feeling of digestive disturbances. Increased diaphoresis.

1944 pollen count 4
1943 pollen count 6

8/28/44 —Slight increase of urine, otherwise less sneezing than previously. 1944 pollen count 56*
1943 pollen count 98

9/21/44 —Did not take the Vitamin C during this period and sneezed more than at the time

9/28/44 —she was taking them.
* Incomplete due to showers.

Clinical Summary

6/2/44 —Nasal mucosa markedly congested; very little nasal space; serous nasal discharge.

6/28/44 —Moderate nasal congestion; nasal fossae show fair degree of space; slight mucoid discharge.

8/7/44 —Nasal mucosa slightly congested; good nasal space; slight mucoid discharge.

8/28/44 —Good nasal passageway; mucosa appears fairly normal; slight mucoid discharge.

9/21/44 —Good nasal space; nasal mucosa appears fairly normal.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

- For how many seasons have you had hay fever?
17.
- Do you have food allergies as well? Yes.
- Do you have asthmatic attacks during the hay fever season? Occasionally.
- When did you start taking the Special Vitamin C tablets? June, 1944.
- When did you first have any hay fever symptoms? Aug. 18, 1944.
- Would you consider your attacks
 - worse
 - same
 - less X
 than previous years?
- How many tablets did you take at the beginning?
3 a day, subsequently 9 a day—altogether 400 tablets.
- Did increasing the dosage give
 - same
 - better X
 results?
- Do you think the Special Vitamin C tablets were
 - no help
 - helpful X

10. Did the tablets cause any irritation of the stomach? Once in a while.

11. Was there any increase in urination after taking tablets aside from hay fever symptoms? Yes.

12. Did you feel generally

- same
- worse
- better X

than previous years?

13. Did you also receive hay fever injections? Yes.

14. Have hay fever injections been helpful in previous years? Yes.

15. Would you consider the Vitamin C tablets modified your hay fever attacks. Yes.

Remarks: Did not take the pills from Sept. 21st to Sept. 28th and missed them and sneezed during that period.

Name: S. H. Occupation: Saleslady,

A. R.
532 W. 143rd Street
New York, N. Y.

History

About five years ago had nasal obstruction. Occasional headache. Last August had hay fever. Frontal headaches. Eyes feel heavy, feel tired. Has trouble with menses. History of hay fever for thirteen years. No allergies to food.

Examination

Mucosa—Vasomotor rhinitis.

Septum—Moderately deflected.

Impacted middle turbinate.

Bilateral hyperplastic ethmoiditis.

Therapy

Turbinectomy in 1933

7/15/44—Started on C.B. pills, 1 T.I.D.

8/1/44 —Slight increase of urination. No irritation of stomach. 1944 pollen count 0
1943 pollen count 0

8/15/44—C.B. pills increased to 3 T.I.D. 1944 pollen count 32
1943 pollen count 25

9/1/44—Increase in urination. Otherwise feeling fine with very little sneezing.

Clinical Summary

8/1/44 —Nasal mucosa slightly engorged; very little nasal discharge; moderate nasal obstruction.

8/15/44—Nasal fossae show good space; mucosa not engorged; very little nasal discharge.

9/1/44 —Nasal mucosa hyperplastic, but shows no vasomotor disturbances; nasal fossae fairly clear; very little nasal discharge.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

- For how many seasons have you had hay fever? 13 years.
- Do you have food allergies as well? No.
- Do you have asthmatic attacks during the hay fever season? No.

4. When did you start taking the Special Vitamin C tablets? Middle of July.
5. When did you first have any hay fever symptoms? End of August.
6. Would you consider your attacks
 - a. worse
 - b. same X
 - c. less
 than previous years?
7. How many tablets did you take at the beginning? 3 a day.
8. Did increasing the dosage give
 - a. same
 - b. better X
 results?
9. Do you think the Special Vitamin C tablets were
 - a. no help
 - b. helpful X
10. Did the tablets cause any irritation of the stomach? No.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? Yes.
12. Did you feel generally
 - a. same
 - b. worse
 - c. better X
 than previous years?
13. Did you also receive hay fever injections? No.
14. Have hay fever injections been helpful in previous years? Never took any.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Remarks: Due to a bad season I was not as well as the past two years.

Name: J. C.

Occupation: Actress.

E. S.

Flushing, L. I. Age 40

History

Hay fever for past twenty years. No food allergies.

Examination

Vasomotor rhinitis.

Therapy

9/2/44—Started C.B. pills, 3 T.I.D. First hay fever symptoms August 15th 1944 pollen count 346 1943 pollen count 233 Patient did not return to office for further treatment but reported by phone that she is feeling much better than she had in previous years while she was taking hay fever injections. None given this year. The C.B. pills seem to modify her attacks a great deal. No irritation of stomach or bladder reported.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? About 20.

2. Do you have food allergies as well? No.
 3. Do you have asthmatic attacks during the hay fever season? No.
 4. When did you start taking the Special Vitamin C tablets? Sept.
 5. When did you first have any hay fever symptoms? Aug. 15.
 6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less X
 than previous years?
 7. How many tablets did you take at the beginning? 9 a day.
 8. Did increasing the dosage give
 - a. same
 - b. better
 results?
 9. Do you think the Special Vitamin C tablets were
 - a. no help
 - b. helpful X
 10. Did the tablets cause any irritation of the stomach? No.
 11. Was there any increase in urination after taking tablets aside from hay fever symptoms? No.
 12. Did you feel generally
 - a. same
 - b. worse
 - c. better X
 than previous years?
 13. Did you also receive hay fever injections? Yes.
 14. Have hay fever injections been helpful in previous years? Yes.
 15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.
- Name: E. S.
Occupation: Housewife.
F. B. S.
2214 64th Street
Brooklyn, N. Y. Age 26
- History*
- Has had hay fever for last 4 years. About 2 weeks ago had nasal obstruction. Has nasal stuffiness, sneezing and running. Had 6 injections of hydrochloric acid for hay fever. Operations—Thyroidectomy 12 years ago.
- Examination*
- | | |
|-------------------|--|
| Septum | —Deflected sharply to the left. |
| Turbinates | —Inferior turbinates hypertrophied. |
| Mucosa | —Hyperplastic—nasal fossae markedly obstructed. |
| Discharge | —Mucoid discharge both middle meati—serous mucoid discharge. |
| Transillumination | —Moderately diminished both sides. |
| Tonsils | —Removed. |
- Therapy*
- 6/3/44—Started hay fever injections.
Started C.B. Pills, 1 T.I.D.

8/15/44—Increase in urination.
Slight irritation of stomach.

1944 pollen count 32
1943 pollen count 25

9/3/44 —First hay fever symptom with very little sneezing. Increased dosage to 3 T.I.D.

1944 pollen count 354
1943 pollen count 106*

9/15/44—Feels better this year than previously; instead of losing weight, patient gained 4 pounds; very little sneezing.

1944 pollen count 75
1943 pollen count 51

*incomplete count due to showers.

Clinical Summary

8/15/44—Nasal mucosa not engorged; moderately good nasal space; very little nasal discharge.
9/3/44 —Nasal engorgement of the mucosa, moderate, with fair nasal space and slight sero-mucinous discharge.
9/15/44—Nasal fossae shows good ventilation; mucosa not engorged; very little nasal discharge.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 8.
 2. Do you have food allergies as well? No.
 3. Do you have asthmatic attacks during the hay fever season? No.
 4. When did you start taking the Special Vitamin C tablets? May 15th.
 5. When did you first have any hay fever symptoms? August.
 6. Would you consider your attacks
 - worse
 - same
 - less Xthan previous years?
 7. How many tablets did you take at the beginning?
3 a day, then increased to 6, then 9 a day.
 8. Did increasing the dosage give
 - same
 - better Xresults?
 9. Do you think the Special Vitamin C Tablets were
 - no help
 - helpful Very.
 10. Did the tablets cause any irritation of the stomach? No.
 11. Was there any increase in urination after taking tablets aside from hay fever symptoms? Yes.
 12. Did you feel generally
 - same
 - worse
 - better Xthan previous years?
 13. Did you also receive hay fever injections? Yes.
 14. Have hay fever injections been helpful in previous years? Not much.

15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Remarks: This year the hay fever attacks started later than any previous year, namely Sept. 3rd. Also, instead of losing weight during the season, I gained about 4 lbs.

Name: F. B. S.

Occupation: Housewife.

Case XXII

P. S.

140 Riverside Drive
New York, New York

History

9/10/43—Sneezing for last two weeks. No previous attacks. Has frontal headache, nasal obstruction. Has itching of eyes. No sore throat.

Examination.

Mucosa—Allergic type — bilateral hyperplastic pan-sinusitis.

Septum = Moderately deflected.

Tonsils—Removed.

Thesaurus

6/7/44 — Started hay fever injections but discontinued before the series was completed as patient

8/5/44 — Started C.B. pills 3 1944 pollen count 0
T.D. 1943 pollen count 0

T.I.D. 1943 pollen count 6
9/15/44—Patient took only a few, perhaps 3 dozen C.B. pills but then not every day. Unable to judge if they were of any help or not. 1944 pollen count 75
1943 pollen count 51

Clinical Summary

8/5/44 —Nasal mucosa moderately congested; nasal fossae partially obstructed; fairly profuse serous discharge; nasal alae reddened and slightly excoriated.

9/15/44—Nasal mucosa still congested; nasal ventilation poor; sero-mucinous discharge.

9/4/44 —Nasal mucosa congested; nasal fossae partially obstructed; moderate serous discharge.

9/25/44—Nasal mucosa moderately engorged; nasal fossae show moderate nasal obstruction; moderate serous discharge.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 7 years.
 2. Do you have food allergies as well? No.
 3. Do you have asthmatic attacks during the hay fever season? Yes.
 4. When did you start taking the Special Vitamin C tablets? Aug. 1.
 5. When did you first have any hay fever symptoms?

6. Would you consider your attacks
 - a. worse X
 - b. same
 - c. less
 than previous years?
7. How many tablets did you take at the beginning?
9 a day.
8. Did increasing the dosage give
 - a. same
 - b. better
 results?
9. Do you think the Special Vitamin C Tablets were
 - a. no help X
 - b. helpful
10. Did the tablets cause any irritation of the stomach?
Don't know.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? No.
12. Did you feel generally
 - a. same
 - b. worse X
 - c. better
 than previous years?
13. Did you also receive hay fever injections? Yes.
14. Have hay fever injections been helpful in previous years? Yes.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Not much.

Remarks: I took only a few of the tablets.

Name: P. S.

Occupation: Dress Manufacturer.

Case XXIII

S. A. S.
275 Central Park West
New York, New York

History

Hay fever for 4 or 5 years.

Examination

Mucosa — Nasal Mucosa moderately hypertrophic.
Buccal mucosa is normal.
Septum — In midline.
Turbinates — Inferior turbinates moderately hypertrophic on both sides.
Tongue — Slightly coated.
Tonsils — Removed, adenoids removed. At the orifice of the right Eustachian tube is some small papillomatous tissue.
Right Ear — Large drum defect occupying posterior half of drum membrane, now healed by scar adherent to the promontory and to the head of the stapes.
Left Ear — Large healed central perforation with calcification of upper portion of drum membrane and retraction.

Therapy

8/1/44 — Allergy testing with
4+ Ragweed and
Timothy. Started on 1944 pollen count 0
C.B. pills, 2 T.I.D. 1943 pollen count 0
9/4/44 — Some sneezing. Dosage increased to 3
T.I.D. No increase

	in urine or stomach irritation.	1944 pollen count 238
		1943 pollen count 45
9/25/44 —	Still sneezing. Patient explains this as due to being exposed more to pollen this year due to military activities.	1944 pollen count 9
		1943 pollen count 4

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? 4 or 5 years.
2. Do you have food allergies as well? Don't know.
3. Do you have asthmatic attacks during the hay fever season? Yes.
4. When did you start taking the Special Vitamin C tablets? August.
5. When did you first have any hay fever symptoms? 5 years ago.
6. Would you consider your attacks
 - a. worse
 - b. same X
 - c. less
 than previous years?
7. How many tablets did you take at the beginning? 6 daily.
8. Did increasing the dosage give
 - a. same X
 - b. better
 results?
9. Do you think the Special Vitamin C tablets were
 - a. no help X
 - b. helpful
10. Did the tablets cause any irritation of the stomach? No.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? No.
12. Did you feel generally
 - a. same X
 - b. worse
 - c. better
 than previous years?
13. Did you also receive hay fever injections? No.
14. Have hay fever injections been helpful in previous years? Did not have any.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? No.

Remarks: I was more exposed to pollen this year because of military training.

Name: S. A. S.

Occupation: Attorney.

Case XXIV

K. T.
44 Metropolitan Oval
New York, N. Y. Age 26

History

Allergic from August to end of hay fever season. Post nasal drip. Occasional headaches. Also has hives.

Examination

Mucosa — Hyperplastic.
Septum — Deflected to right.

Buccal mucosa—Normal.
 Teeth —Calcium deficiency.
 Tongue —Mucosa thickened.
 Tonsils —Removed.
 Ears —Negative.

Therapy

7/25/44	Allergy testing 4+ to Ragweed and Timothy.
8/7/44	Started C.B. pills, 1 T.I.D.
8/20/44	First hay fever symptoms with very little sneezing. Increased dosage to 3 T.I.D.
9/1/44	Slight increase in urination.
9/10/44	No sneezing after increase of dosage. Much better this season than previously.

1944 pollen count 4
1943 pollen count 6
1944 pollen count 40
1943 pollen count 66
1944 pollen count 106
1943 pollen count 235
1944 pollen count 50
1943 pollen count 32

Clinical Summary

8/20/44	Moderate nasal engorgement; moderate nasal obstruction; increased mucoid discharge.
9/1/44	Less nasal obstruction; mucosa slightly engorged; slight mucoid discharge.
9/10/44	Fair nasal space; slight mucosal congestion and slight mucoid discharge.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

- For how many seasons have you had hay fever? 15.
- Do you have food allergies as well? Yes, slightly.
- Do you have asthmatic attacks during the hay fever season? No.
- When did you start taking the Special Vitamin C tablets? August 7.
- When did you first have any hay fever symptoms? August 20.
- Would you consider your attacks
 - worse
 - same
 - less
 than previous years?
- How many tablets did you take at the beginning? 3 a day.
- Did increasing the dosage give
 - same
 - better
 results?
- Do you think the Special Vitamin C tablets were
 - no help
 - helpful
- Did the tablets cause any irritation of the stomach? No.
- Was there any increase in urination after taking tablets aside from hay fever symptoms? Yes.
- Did you feel generally
 - same
 - worse
 - better
 than previous years?

- Did you also receive hay fever injections? No.
- Have hay fever injections been helpful in previous years? No.
- Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.
Name: K. T.
Occupation: Secretary.

M. O. 117-01 Park Lane S.
Kew Gardens, N. Y. Age 3

History

Since the beginning of August has been having nasal obstruction, sneezing and nasal discharge, particularly bad at night and disturbing the baby's sleep.

Examination

Mucosa —Swollen, occluding almost completely both nasal fossae.
Turbinates—Inferior turbinates in contact with septum on both sides.
Tonsils —Hypertrophied and diseased.

Therapy

9/6/44 —Child came to office with typical hay fever symptoms. Sneezing, running eyes and nose. Tested for ragweed 4+ results. Has had symptoms since 8/20/44. Started with C.B. pills, 2 T.I.D. 1944 pollen count 312
1943 pollen count 60

9/20/44 —Very little sneezing. Nose and eyes not running. Child greatly relieved by the C.B. pills. 1944 pollen count 10
1943 pollen count 48

Clinical Summary

9/20/44 —Nasal passageway clear; very little nasal discharge; inferior turbinates appear normal.

B. W.

734 E. 6th Street
New York, N. Y. Age 27

History

Hay fever; post nasal discharge. Hay fever for the past fifteen years, very severe during the last few seasons. Has been unable to work regularly for a number of years during the hay fever season. Recurrent frontal headaches.

Examination

Mucosa —Hyperplastic.

Turbinates—Hypertrophied, both middle turbinates have been partially resected, and a partial anterior ethmoidectomy has been performed.

Septum —In mid position.
Tonsils —Removed.

Therapy

7/20/44—Started ragweed injections.

8/22/44—Started C.B. pills, 2 T.I.D. Allergy testing: ragweed 4+, dust 2+, timber 4+, feathers 2+. Also some food allergies.

8/31/44—Very little sneezing. Increased dosage to 3 T.I.D.

9/6/44—Feeling better than at any other time. States of slight increase in urination.

1944 pollen count 93
1943 pollen count 32

1944 pollen count 131
1943 pollen count 236

1944 pollen count 312
1943 pollen count 60

Clinical Summary

8/22/44—Nasal mucosa acutely congested; profuse serous discharge; severe nasal obstruction.

8/31/44—Nasal mucosa slightly congested; nasal fossae fairly clear; very little nasal discharge.

9/6/44—Nasal fossae show good space; inferior turbinates not congested; nasal mucosa not engorged.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? Two.
2. Do you have food allergies as well? Yes.
3. Do you have asthmatic attacks during the hay fever season? No.
4. When did you start taking the Special Vitamin C tablets? Aug. 22.
5. When did you first have any hay fever symptoms? 2 years ago.
6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less
 than previous years?
7. How many tablets did you take at the beginning? 3 a day. Subsequently 6 a day, altogether 300 tablets.
8. Did increasing the dosage give
 - a. same
 - b. better
 results?
9. Do you think the Special Vitamin C tablets were
 - a. no help
 - b. helpful
10. Did the tablets cause any irritation of the stomach? No.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? Yes.
12. Did you feel generally
 - a. same
 - b. worse
 - c. better
 than previous years?

13. Did you also receive hay fever injections? Yes, before Vitamin C tablets.
14. Have hay fever injections been helpful in previous years? Yes.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Remarks: Also received dust injections.

Name: B. W.

Occupation: Printing and binding.

M. W.
Mt. Vernon, New York Age 46

History

Has had severe hay fever for last twenty-five years. Has received pollen injection for desensitization for last fifteen years with little benefit. Went to New York Hospital for injections.

Examination

Mucosa—Chronically thickened and hyperplastic—septal mucosa hypertrophied.

Turbinates—Both middle and inferior turbinates hypertrophied.

Septum—in mid position.

Tonsils—Removed

Therapy

7/15/44—Started C.B. pills, 1 T.I.D.

Patient did not return to office but reported by letter that she has felt better this season for the first time in 25 years. Her first symptoms on August 25th; during this season she had only about 4 or 5 very bad attacks but with no asthmatic attacks. States of no irritation to stomach or bladder. Dosage increased in 1 month's time to 2 T.I.D.

QUESTIONNAIRE ON VITAMIN C IN ALLERGY

1. For how many seasons have you had hay fever? About 25 years.
2. Do you have food allergies as well? No.
3. Do you have asthmatic attacks during the hay fever season? Sometimes.
4. When did you start taking the Special Vitamin C tablets? July 15, 1944.
5. When did you first have any hay fever symptoms? On or about August 25, 1944.
6. Would you consider your attacks
 - a. worse
 - b. same
 - c. less
 than previous years?
7. How many tablets did you take at the beginning? 3 a day, then 6 a day.
8. Did increasing the dosage give
 - a. same
 - b. better
 results?

9. Do you think the Special Vitamin C tablets were
 - a. no help
 - b. helpful
10. Did the tablets cause any irritation of the stomach? No.
11. Was there any increase in urination after taking tablets aside from hay fever symptoms? No.
12. Did you feel generally
 - a. same
 - b. worse
 - c. better
 than previous years?
13. Did you also receive hay fever injections? No.
14. Have hay fever injections been helpful in previous years? No.
15. Would you consider the Vitamin C tablets modified your hay fever attacks? Yes.

Remarks: I have only had about 4 or 5 very bad attacks this season due to the Vitamin C tablets. I must emphasize the fact that I felt better this season, for the first time in 25 years.

Name: M. W.

Occupation: Housewife.

A supplement of these clinical results is presented with the tabulation of the results obtained in one hundred cases of the common cold and vasomotor rhinitis. In view of frequent association of nasal pathology with nasal allergy, the benefit derived from the calcium cevitamate assumes a double significance, and emphasizes the therapeutic value of vitamin C in large doses. In this latter group on one hundred cases employing calcium ascorbate instead of the vitamin CB tablets as previously described, the therapeutic effect can be attributed essentially to the vitamin C since calcium gluconate has not been shown to be of any value in either the common cold or allergic rhinitis. The antihistamine effect of calcium ascorbate is however, somewhat higher than vitamin C alone.

The great prevalence of allergy prompts us to inquire into the possible etiologic features of this disturbance. It has been well established that allergy is a biochemical derangement intimately related to histamine balance. Today we realize that in these biochemical disturbances nutritional deficiencies both in amino acids and vitamins plays a very significant if not dominant role. In the light of the demonstrated antihistamine effect of vitamin C, it behooves us to consider the widespread distribution of vitamin C deficiency.

Crane, Woods, Waters and Murphy determined the level of ascorbic acid in the blood plasma of eighty-six rural children in grade schools in a northern Maine village in the autumn and again in the spring. The plasma of only two of the eighty-six children contained as much as 0.8 mg. per cent of ascorbic acid in both seasons and dietary studies indicated that probably not more than one child in seven was eating a good source of vitamin C a day. In the autumn the ascorbic acid content of the plasma of 28 per cent of the children was below 0.4 m, per cent; in the spring 55 per cent were in this category. An association between low ascorbic acid in plasma and an inflammation of the

gums was observed. In the autumn 29 per cent of the children had inflamed gums but by spring the condition had grown worse and 51 per cent had inflamed gums. Administration of ascorbic acid to 41 of the children with inflamed gums indicated that insufficiency of vitamin C probably was a factor in this condition; improvement followed within three weeks in the case of two-thirds of the children treated.

Under the auspices of the Rockefeller Foundation, studies of nutritional status are being made in two rural communities in the South. One was undertaken in 1940 in a rural mill town in North Carolina, in co-operation with the Health Department and Duke University. The other, in co-operation with Vanderbilt University, was begun the year before in a rural area of Tennessee. At the 18th annual conference of the Milbank Memorial Fund Youmans reported findings from the first 129 families studied in the latter investigation. Twenty-five per cent of 411 persons examined in a visual dark adaptation test gave values regarded as definitely abnormal, indicative of vitamin A deficiency; 11 per cent of 502 persons tested had less than 0.3 mg. ascorbic acid per 100 ml. blood plasma, values considered to be unquestionably abnormal; and 26 per cent of 498 individuals examined had lower hemoglobin and 44 per cent lower red cell counts, than current minimum normal values for the sex and age groups studied. Evidence of protein deficiency was noted in 20 per cent of 455 individuals. Though incomplete and preliminary, these data indicate that a large proportion of the population included in the study is poorly nourished with respect to a number of essential nutrients.⁴ In addition to the cases noted above as definitely abnormal, an even larger proportion was regarded as border-line, probably subnormal, cases.

Minot and co-workers, in determining the ascorbic acid content of the serum of "normal" children (patients without serious or significant disease attending the pediatric clinic of Vanderbilt hospital), found that about half of those examined in the age range three to fifteen years had ascorbic acid values of 0.7 mg. or more per 100 ml. of serum. These values were considered indicative of a fairly satisfactory state of vitamin C nutrition. However, of the entire group of 380 children under fifteen years of age examined, about 35 per cent of those tested during the winter and about 20 per cent tested during the summer had ascorbic acid values under 0.3 mg. per 100 ml. of blood serum; these values are considered indicative of serious deficiency. Less seasonal variation in values was found among children under three years of age than among those from three to fifteen years, a fact explained by the lesser variation in diets of the younger children. Relatively more sick than well children were found with serum low in ascorbic acid. Although the ascorbic acid levels of many children were low enough to be associated with a marked degree of deficiency of vitamin C in the tissues, a diagnosis of scurvy was rarely made, notwithstanding careful study of roentgenograms and a search for other clinical evidence. Clinical scurvy was not found even among children whose ascorbic acid levels were known to remain persistently below

HIGH DOSAGE VITAMIN C IN ALLERGY

Name	Sex	Age	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Remarks
1. R. B.	M	19	yes	occasionally		7th	Sum- mer 1925	less but severe	3	no in- crease	a	no quest- ionable	b	yes	ques- tion- able	no	Combined with desensitization	
2. B. B.	F	1	yes	no		7th	5th	first	3, 6, 9.	b	b	slight heart burn	first Sea- son	no	first Sea- son	yes	C B Pills only	
3. S. C.	F	12	?	?		? 8/20/ 44	treat- ment stop- ped		3	hives around eyes	b	yes	yes	a	no	no	yes C B Pills only	
4. G. P. C.	F	0	yes	yes		?	?	c	1	don't know	b	no	no	c	yes	no	yes Combined with desensitization	
5. J. C.	F	8	yes	yes		8th	8th	c	3	b	b	no	possi- bly	c	yes	First sea- son	yes Combined with desensitization	
6. S. D.	M	3	no	no		?	?	c	3	no in- crease	b	yes	no	c	yes	yes	yes Combined with desensitization	
7. R. F.	M	2	no	no		6th	5th	b	3	a	b	no	no	c	yes	yes	yes Combined with desensitization	
8. B. G.	M	2	no	yes		9th	?	b	9	no in- crease	b	no	no	c	no	no	yes C. B. Pills only	
9. N. H.	F	2	yes	yes		?	?	c	6 9	a	b	no	no	c	no	no	yes C. B. Pills only	
10. M. J. H.	M	35	no	no		9th	35	c	9	b	b	no	no	c	no	yes	yes C B Pills only	
11. E. C. H.	F	1	yes	yes		8th	?	c	9	no in- crease	b	no	no	c	no	first	yes C B Pills only	
12. E. H.	M	12	yes	no		5th	9th	c	3	b	b	no	yes	c	no	no	yes C B Pills only	
13. E. L.	M	11½	4	yes	no	7th	6th	c	3	a	b	no	no	c	no	yes	yes C B Pills only	
14. W. L.	M	46	no	yes		6th	8th	c	3	b	b	no	yes	c	yes	yes	yes Combined with desensitization	
15. M. M.	M	15	no	no		9th	8th	c	3	b	b	yes	yes	c	no	no	yes C B Pills only	
16. G. E. P.	F	2	yes	yes		8th	all year	c	6 9	b	b	yes	no	c	no	none	yes C B Pills only	
17. R. R.	M	6	2	yes	no	7th	8th	c	3	no in- crease	a	no	no	c	no	no	no C B Pills plus nucleic acid powder	
18. S. R.	F	17	yes	occa- sion- ally		6th	8th	c	3 9	b	b	sometime	yes	c	yes	yes	yes Combined with desensitization	
19. A. R.	F	13	no	no		7th	8th	b	3 9	b	b	no	yes	c	no	no	no C B Pills only	
20. P. S.	M	7	no	yes		8th	?	a	9	no in- crease	a	don't know	?	b	yes	yes	yes Combined with desensitization	
21. E. S.	F	20	no	no		9th	8th	c	9	no in- crease	b	no	no	c	yes	yes	yes Combined with desensitization	
22. A. S.	M	4	?	yes	or 5	8th	?	b	6	a	a	no	no	a	no	none	yes C B Pills only	

Name	Sex	Age	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Remarks
23. F. B.	F	8	no	no		5th	8th	c	3	b	b	no	yes	c	yes	not much	yes	Combined with desensitization
24. K. T.	F	15	yes	no		8th	8th	b	3	b	b	No	yes	c	no	no	yes	C. B. Pills only
25. M. U.	F	1	yes	?		9th	8th	1st Sea- son	2	no	b	no	yes	1st Sea-	no	no	yes	C. B. Pills only
26. B. W.	F	2	yes	no		8th	?	c	3	b	b	no	yes	c	yes	yes	yes	Combined with desensitization
27. F. W.	F	25	no	yes		7th	8th	c	3	b	b	no	no	c	no	no	yes	C. B. Pills only

Calcium Ceritamate In Acute Rhinitis

Case Pat- No. ident	Sex	Date	Diagnosis	Comment	Case Pat- No. ident	Sex	Date	Diagnosis	Comment
1 B. B.	M	3/24, 1937	Acute cold	Marked im- provement	18 L.L.M.	M	5/10, 1937	Acute rhinitis	Complete re- lief
2 C.G.	F	4/5, 1937	Acute cold	Complete re- lief	19 G. B.	F	3/1, 16, 4/6, 1937	Acute cold	Complete re- lief
3 E. K.	F	4/5, 1937	Acute cold	Complete re- lief	20 H. C.	F	3/26, 21, 1937	Bilateral max- illary sinusitis	Marked im- provement
4 I. G.	F	4/5, 1937	Acute cold	Complete re- lief	21 R. M.	F	3/21, 1937	Acute cold	Complete re- lief
5 I. G.	F	4/5, 1937	Acute cold Rt. ethmoiditis	Marked im- provement	22 J.O.D.	M	3/20, 1937	Acute cold	Complete re- lief
6 H. S.	F	4/1, 2, 5, 7, 1937	Grippe, left sphenoiditis	Marked im- provement	23 J. N.	M	3/23, 24, 31, 1937	Bilateral max- illary sinusitis	Marked im- provement
7 P. D.	M	4/6, 1937	Aphthous stom- atitis, Acute cold	Complete re- lief. Stomat- itis dis- appeared after one injection.	24 E. S.	F	3/25, 1937	Acute cold	Complete re- lief
8 G. B.	M	4/7, 1937	Acute laryn- gitis	Marked im- provement	25 R. G.	F	3/28, 1937	Acute cold	Complete re- lief
9 L. G.	F	4/7, 12, 1937	Acute cold	Complete re- lief	26 A. S.	M	10/21, 25, 11/13 12/21, 1936; deflected sep- 1/15, 29, 2/24, tum, 25, 1937	Acute rhinitis; Marked im- provement	
10 D. S.	F		Bilateral max- illary and eth- moid sinusitis	Improvement noted with caecil injec- tion.	27 C. R.	F	10/22, 11/12, 1936	Acute rhinitis	Completely relieved
11 L. K.	M	11/9, 11, 1936	Acute rhinitis	Marked im- provement	28 H. R.	M	10/23, 26 11/27, 30, 1936; Bilateral max- 1/8, 18, 22, 29, illary ethmoid- 2/24, 1937	Acute symp- toms relieved Sinusitis im- proved	
12 P. S.	F	11/10, 15, 12/7 1936, 3/31, 1937	Bilateral eth- moiditis	Marked im- provement	29 N. K.	F	10/30, 11/2, 4, 6, 11, 12/19, 1936	Vasomotor rhinitis, severe	Marked im- provement
13 W. H.	M	4/20, 1937	Acute cold	Complete re- lief	30 E. J.	F	11/2, 9, 13, 17 Bilateral eth- moiditis	1936	Marked im- provement
14 R. R.	F	4/27, 1937	Bilateral eth- moiditis	Moderate improvement.	31 S.W.	F	11/2, 1936	Acute cold	Complete re- lief
15 F. G.	F	4/27, 1937	Bilateral eth- moiditis	Marked im- provement	32 W.J.R.	M	11/3, 9, 23, 1936	Acute rhinitis	Marked im- provement
16 D.D.D.	M	4/28, 1937	Acute rhinitis	Marked im- provement	33 A. S.	F	11/3, 9, 11, 1936	Bilateral eth- moiditis	Deflected sep- Marked im- provement
17 M. B.	F	5/3, 7, 1937	Bilateral eth- moiditis	Marked im- provement					

Case No.	Patient	Sex	Date	Diagnosis	Comment	Case No.	Patient	Sex	Date	Diagnosis	Comment
34	S. T.	F	10/29, 11/3, 10, 25, 1936	Bilateral eth- moiditis; spheno- opalatine ganglion neu- ralgia	Marked im- provement	53	C. S.	M	10/26, 28, 1936	Acute cold, Bilateral eth- moiditis	Marked im- provement
35	G. F.	M	11/4, 1936	Acute cold	Complete re- lief	54	S. C.	F	10/26, 11/9, 1936	Acute rhinitis	Marked im- provement
36	A. G.	M	11/4, 1936	Acute rhinitis	Complete re- lief	55	R. S.	F	10/27, 30, 1936	Acute cold Hypertrophic turbinate	Marked im- provement
37	S. R.	M	10/16, 1936	Acute rhinitis	Relieved completely	56	M. R.	F	10/27, 1936	Acute cold	Marked im- provement
38	S. H.	M	10/15, 23, 26 3/10, 12, 1937	Acute rhinitis Bilateral eth- moiditis	Relieved completely	57	B. B.	F	10/18, 1936	Acute cold	Complete re- lief
39	E. L.	M	10/20, 1936	Acute rhinitis	Marked im- provement	58	Mr. G.	M	10/28, 1936	Bilateral eth- moiditis	Marked im- provement
40	T. C.	F	10/20, 23, 27 11/9, 17, 12/9, 13, 21, 1936; 1/5, 8, 1937	Bilateral eth- moiditis	Marked im- provement	59	B. N.	M	10/28, 11/2, 9, 23, 12/7, 21, 1936; 1/4, 15, 1937	Acute rhinitis	Complete relief
41	L. A.	F	10/20, 23, 26, 11/7, 12/11, 1936; 2/27, 1937	Acute rhinitis, deviated sep- tum, bilateral ethmoiditis	Relieved of acute attacks. Sinusitis im- proved.	60	F. W.	M	4/1, 1937	Acute cold	Complete relief
42	F. R.	F	10/10, 21, 1936	Acute rhinitis	Relieved completely	61	L. L.	M	4/9, 1937	Vasomotor Rhinitis	Marked im- provement
43	A. C.	M	10/21, 24, 26, 11/6, 9, 11, 12, 1936	Acute rhinitis Bilateral eth- moiditis	Marked im- provement	62	H. W.	M	4/9, 12, 19, 1937	Acute cold	Marked im- provement
44	F. S.	M	10/21, 25, 28, 12/14, 1936; 1/27 3/10, 12, 4/7, 1937	Acute rhinitis, left pan-sinus- itis; left radi- cal pan-sinus operation four years ago	Marked im- provement	63	A. C.	F	4/10, 1937	Bilateral eth- moiditis Acute rhinitis	Marked im- provement
45	I. E.	M	10/21, 1936	Acute rhinitis	Relieved completely	64	M. R.	F	4/10, 13, 1937	Acute cold	Complete relief
46	E. E.	F	10/21, 26, 11/4, 1936	Acute rhinitis Bilateral eth- moiditis	Completely relieved	65	R. M.	M	4/3, 1937	Acute cold	Improved after one injection
47	L. C.	F	10/22, 26, 29, 11/23, 27, 1936	Acute rhinitis Bilateral eth- moiditis	Completely relieved	66	R. L.	F	4/5, 15, 1937	Bilateral eth- moiditis	Marked im- provement
48	J. W.	M	11/9, 12, 1936	Acute rhinitis	Marked im- provement	67	D. L.	M	4/13, 1937	Acute rhinitis	Marked im- provement
49	A. F.	F	10/23, 26, 11/17 23, 1936	Acute rhinitis Nasal allergy	Marked im- provement	68	K. M.	M	4/13, 1937	Acute rhinitis	Complete relief
50	A. K.	F	10/26, 1936	Acute rhinitis	Marked re- lief	69	N. F.	F	4/11, 13, 1937	Acute cold	Complete relief
51	B. S.	F	10/26, 1936	Acute rhinitis	Completely relieved	70	S.L.R.	M	4/19, 1937	Acute cold	Complete relief
52	L. S.	F	10/26, 1936	Acute rhinitis	Marked im- provement	71	S. F.	M	4/1, 19, 1937	Acute cold	Complete relief
				right maxil- lary sinusitis, old radical op- eration		72	M. H.	M	4/19, 23, 27, 30	Bilateral Polypoid, asthma, Max- illary sinu- sitis	Marked im- provement
						73	G. N.	M	4/24, 1937	Bilateral eth- moiditis	Complete relief
						74	E. H.	F	4/26, 29, 1937	Acute cold	Complete relief
						75	J. F.	M	8/18, 1937	Allergic rhinitis	Marked im- provement

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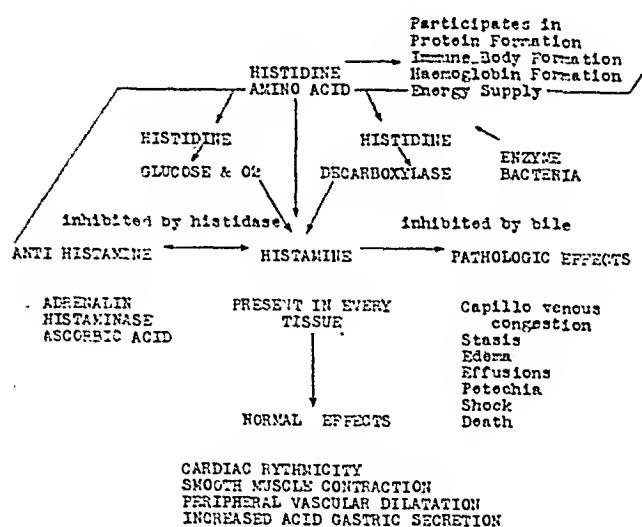
<i>Case Pat-</i> <i>No.</i>	<i>Patient</i>	<i>Sex</i>	<i>Date</i>	<i>Diagnosis</i>	<i>Comment</i>	<i>Case Pat-</i> <i>No.</i>	<i>Patient</i>	<i>Sex</i>	<i>Date</i>	<i>Diagnosis</i>	<i>Comment</i>
76	A. B.	F	8/18, 1937	Acute rhinitis Acute otitis, grippe type	Improved. No paracentesis	91	I. B.	F	10/28, 11/6, 16, 1936	Deviated septum Bilateral ethmoiditis, acute rhinitis	Marked improvement
77	M. R.	F	6/25, 28, 1937	Acute rhinitis	Complete relief	92	R. T.	M	10/28, 11/2, 16, 1936	Sinusitis; bilateral maxillary sinusitis. Asthma	Marked improvement in asthma and sinusitis
78	J. B.	M	10/28, 1937	Acute cold	Complete relief	93	C. N.	M	10/30, 1936	Acute rhinitis	Completely relieved
79	A. S.	M	7/8, 13, 8/16, 1937	Nasal allergy; bilateral maxillary & ethmoidal sinusitis	Marked improvement	94	C. A.	M	10/30, 1936	Acute rhinitis	Completely relieved
80	B. L.	F	7/12, 16, 1937	Acute rhinitis & bronchitis	Marked improvement	95	A. M.	M	10/31, 11/7, 21, 1936	Allergic vasomotor rhinitis	Marked improvement
81	I. L.	F	7/17, 8/9, 25, 9/16, 20, 24, 27, 10/1, 3, 7, 15, 18, 19, 1937	Bilateral ethmoiditis	Moderately improved	96	R. M.	F	11/1, 9, 19, 12/2, 20, 1936, 1/5, 10, 15, 2/19, 25, 3/16, 1937	Post-nasal drip, Bilateral ethmoiditis	Marked improvement
82	L. S.	F	7/17, 23, 8/4, 6, 13, 20, 9/8, 12, 28, 1937	Bilateral ethmoiditis	Marked improvement	97	D. K.	F	10/14, 20	Allergic rhinitis, polypoid pan-sinusitis, Deflected septum	Allergy improved greatly, sinusitis recurred, radical operation
83	L. I.	M	4/9, 1927	Allergic rhinitis	Marked improvement	98	N. G.	F	7/16, 9/27, 10/25, 1937	Bilateral maxillary sinusitis, severe asthma, nasal allergy	Asthma completely relieved, sinusitis markedly improved
84	A. C.	F	4/10, 1937	Bilateral ethmoiditis	Marked improvement	99	J. S.	F	6/28, 7/14, 10, 20, 23, 1937	Bilateral maxillary ethmoid sinusitis, severe asthma, nasal allergy	Asthma markedly improved, sinusitis markedly improved
85	S. F.	M	4/1, 19, 1937	Acute cold, post-nasal drip	Marked improvement	100	J. G.	M	8/1, 21, 24, 31, 9/1, 3, 16, 25, 10/2, 9, 16, 25, 30, 1937	Bilateral ethmoid sinusitis, nasal allergy, asthma	Asthma completely relieved, nasal allergy relieved sinusitis markedly improved
86	R. L.	F	4/5, 17, 1937	Bilateral ethmoiditis, sinusitis	Moderately improved						
87	F. W.	F	11/7, 1936	Acute cold	Complete relief						
88	L. S.	M	11/7, 9, 1936	Acute cold	Complete relief						
89	M. R.	M	11/7, 1936	Acute cold	Complete relief						
90	O. F.	M	10/28, 1936	Acute rhinitis	Complete relief						

0.2 mg. per 100 ml. of serum. The authors suggest that diets that are simultaneously deficient in calories and several other essential food factors may suppress the typical manifestations of deficiency; such low levels of ascorbic acid in otherwise adequately nourished persons might cause obvious scurvy. The investigators call attention to the lack of energy, poor appetite, mental apathy, and generally retarded development that characterized the children. These symptoms probably reflect not only a shortage of vitamin C, but diets that are inadequate in many respects.

Macy and associates observed that infants who were receiving a limited and constant supply of the vitamin showed no signs of scurvy normally, but when they were subjected to the added stress of minor infections, indications of clinical scurvy appeared. Later the signs of scurvy disappeared spontaneously when the effect of the infection had passed. The frequency of hay fever developing on a background of chronic sinusitis is so common that a relationship can hardly escape observation. A connection between chronic infection, nutritional deficiency and allergy has often been implied and may now be formulated.

In the light of these findings, it is possible that where nutritional deficiencies beside that of vitamin C occur, the administration of ascorbic acid alone may not be adequate to achieve proper histamine balance and freedom from allergy. It does not appear that the correction of subclinical vitamin C deficiency may play a very important role in elevating the threshold of allergic sensitivity. From this angle, allergy may be classified among the ever increasing list of nutritional deficiency diseases.

The experimental work undertaken to demonstrate the position of vitamin C among the physiologic forces involved in allergy showed its role as a histamine antagonist. This was accomplished through the microscopic observation of bronchiolar reactions to histamine and antihistamine drugs. As a result of this work, the following scheme was developed. The experiment is described in detail to facilitate future studies by other investigators.



The object of the experiment was to secure a viable section of bronchiole. This was accomplished by fixing the lung of the rabbit in gelatin, chilling it and then cutting a thin section of a bronchiole, which was kept in Ringer-Locke dextrose solution. The section was mounted on a ring so that when the gelatin was dissolved out the reactions of the bronchiole could be observed under the microscope and drawn to size. The whole procedure was conducted with adequate controls to assure the viability of the bronchiolar sections.

I first observed the technic of the microscopic study of bronchiolar reactions in the laboratory of Dr. H. D. Pease, who had constructed an ingenious microscope platform that permitted maintenance of a water bath of constant temperature for the ordinary Petri dish. This could readily be elaborated for a series of microscopes. In general, the technic of Sollmann and Gilbert was used as follows: Each of the following substances was dissolved separately in 500 cc. of water:

	Gm.
Sodium chloride	31.5
Potassium chloride	1.47
Calcium chloride	0.84
Sodium bicarbonate (NaHCO_3)	1.15

The solutions were mixed and diluted to 3.5 liters. On the day of use, dextrose, 1 gm. per liter, was added. Substances to be tested which are sufficiently soluble that a dilution of 1:50 is adequate are made up in distilled water. Those which are less soluble are made up in Ringer-Locke solution.

The animal was killed by intravenous injection of air. The skin was removed from the ventral portion of the abdomen, the thorax and the neck. A midline incision was made from the middle of the abdomen, to the diaphragm. Lateral incisions were made just posterior to the diaphragm toward the sides of the body.

The diaphragm was punctured on each side, allowing the lungs to collapse. The ventral thoracic wall was removed, longitudinal cuts being made along the sides of the thorax anterior to the first pair of ribs. Care was taken not to cut the large axillary veins. A hemostat should be used on any small vessels which are accidentally cut. The first rib and the episternum were carefully removed, carrying with them the ventral neck muscles. The trachea was cut and a cannula inserted, which was held in place with hemostats. The lungs were filled to approximately normal expansion with gelatin (approximately 15 c. of warm 10 per cent gelatin dissolved in Ringer-Locke solution for each kilogram of body weight). The inferior vena cava was clamped with a hemostat, and the lungs, heart and trachea were removed and placed in ice-cold Ringer-Locke solution (approximately 150 cc.). The organs were placed in the freezing compartment of the refrigerator for one to one and a half hours.

The two large lobes of the lung were trimmed to approximately one-half size and thin sections of tissue cut across the bronchiole. These sections should be as thin as possible (0.5 to 1 mm. in thickness). The sections were placed in the cold Ringer-Locke solution in which the lungs were kept. The sections were

kept ice cold until each one was used.

If the substance to be tested was to be diluted, 49 cc. of Ringer-Locke solution was placed in the special dishes (9 cm. Petri dishes, in the center of which a ring of cork with a central opening, approximately 5 cm. in diameter, was cemented with beeswax). The section to be used was pinned out with the bronchiole over the opening of the cork. The sections should not be stretched but should be pinned out flat. The dish was placed on the warm stage and the contents of the dish allowed to warm to 37°C., the section being agitated by means of a stream of Ringer-Locke solution from a small pipet. Camera lucida drawings of the bronchiolar lumen were made until it was of constant size (this usually took ten to fifteen minutes). The test solution was added near the edge of the Petri dish and mixed with a pipet. Then a small amount of fluid in the dish was picked up with the pipet and allowed to run out gently over the tissue. Camera lucida drawings were made as indicated by the reaction of the bronchiole.

In tests designed to show possible antagonism between two substances it was found that the second substance should generally be added about five minutes after the first. The drawings made for each test were dated and a number assigned to each. Each drawing was labeled with the exact time of day, and later these times were translated into terms of minutes which elapsed after the section was put into the dish. These drawings were filed as a permanent record.

Computation of Results:—The area of the bronchiolar lumen was measured in arbitrary units by means of a polar planimeter. The area just before the addition of the first substances to be tested was taken as 100 per cent, and was called the original area. Reactions were expressed as percentages of this original area which remained.

The animals used were white New Zealand rabbits, partially standardized as to age, weight, health and environment. Five animals were prepared and used as described.

The concentration of the solution was kept equal for all comparative tests. The solution of histamine was made up with 100 mg. of histamine hydrochloride to 100 cc. of Ringer-Locke solution. The dilution factor for all solutions of test substances was 1:50, giving with the histamine solution a 1:50,000 concentration.

Experiments 1 and 2 for each day were made as controls. The experiments were arranged in the order of the days on which they were conducted so that the daily controls could be checked against the day's experiments. For each of five groups a new animal was killed, and the experiments and the controls were run simultaneously.

The purpose of the experiment was to produce contraction of the bronchiole by adding histamine hydrochloride to the Ringer-Locke-dextrose solution to obtain a 1:50,000 concentration. After the contraction due to the histamine was established, and at a fixed interval, the substance to be tested for histamine antagonism was added. Those substances which antagonize histamine allowed the bronchiole to relax and in

some instances continued the dilatation above normal. The control tests also showed that there was a spontaneous tendency for the histamine effect to diminish, with a secondary histamine contraction after about fifteen minutes. As a countercheck for histamine antagonism, therefore, two sets of tests were run. In one series, the substance to be tested was added after the histamine contraction had occurred, and the effect was noted. In the other, histamine contraction was produced, the substance added and the histamine antagonism noted; then histamine was again added to see whether the histamine antagonism of the substance would prevent further histamine effect. With substances having histamine-antagonistic properties, then, there would be no or little contraction of the bronchiole on the secondary addition of histamine. The controls uniformly showed a secondary contraction when the histamine was added for the second time. This double checking system thus provided useful information.

RESULTS OF INVESTIGATION

Group 1—Experiments 1 and 2: These tests were conducted to establish normal as well as histamine controls and a subsequent histamine control after twenty-four minutes. Results for 6 normal and 6 histamine controls were plotted and normal and histamine curves established.

On the day of these experiments the normal control maintained a fairly steady bronchiolar lumen, with only gradual contraction. The histamine control showed rapid contraction of the bronchiole with recovery and a second contraction under the continued action of the histamine, thus causing a secondary drop after seventeen minutes.

Experiments 3 and 4: These tests were conducted with the same tissues as those used in experiments 1 and 2. When sodium ascorbate was added after the histamine recovery was slower than in the control, but the histamine antagonism was evident on the addition of the second dose of histamine hydrochloride after fourteen minutes. There was no secondary histamine contraction.

Experiments 5 and 6: The histamine antagonism of vitamin C alone was evident. Here, again, there was a somewhat slower recovery of the bronchiolar lumen, and recovery was maintained, even after a second dose of histamine, although there was a slight contraction for two minutes.

Summary: The sodium ascorbate and vitamin C did not influence the speed of recovery from histamine contraction but did produce antagonism to the second dose of histamine hydrochloride.

Group 2.—On this day controls showed that the bronchiolar lumen maintained its normal size for the whole thirty minutes. The histamine response was strongly active after thirty minutes, indicating that a secondary histamine contraction was obtainable after exposure for this period.

Experiments 3 and 4: Normal recovery from the effect of histamine hydrochloride was slightly inhibited by ephedrine sulfate, indicating that the drug had a slight constricting action on the bronchiole, with little

or no antagonism to the second dose of histamine.

Experiments 5 and 6: Ephedrine ascorbate produced prompt recovery from a sharper histamine contraction than that showed in the control with maintenance of a good level of histamine antagonism after the second dose.

Experiments 7 and 8: With ephedrine hydrochloride there was a decidedly increased histamine contraction as compared with the response with either ephedrine ascorbate or ephedrine sulfate, as well as delayed recovery. Ephedrine hydrochloride is therefore a bronchiole constricting agent with no histamine antagonism.

Summary: Ephedrine sulfate caused slight inhibition of recovery from histamine hydrochloride, with little or no antagonism to the second dose of histamine. With ephedrine ascorbate there was quick recovery from histamine and fair antagonism to the second dose of histamine. With ephedrine hydrochloride there was an increase in histamine contraction and no histamine antagonism, rather constriction.

Group 3.—Controls for this day showed normal maintenance of the bronchiolar lumen for thirty minutes and an active secondary response to histamine hydrochloride after thirty minutes.

Experiments 3 and 4: Experiments conducted with calcium ascorbate showed a sharp recovery after the first histamine contraction, followed by a moderate drop and a moderate rise after the second dose of histamine. This was more rapid than the response with either vitamin C alone or sodium ascorbate.

Experiments 5 and 6: Calcium gluconate showed no histamine antagonism; in fact, it prolonged the action of the drug. The bronchiole did not recover from the histamine contraction for the whole thirty minutes.

Summary: Calcium gluconate not only did not antagonize histamine hydrochloride, but, in fact, increased contraction of the bronchiole to the drug. Calcium ascorbate, on the other hand, antagonized histamine, and the response was quicker than that to either vitamin C alone or sodium ascorbate. This is significant in view of the conflicting claims made for calcium in the treatment of asthma. It appears from this experiment that the synergistic effect of vitamin C on calcium may be the all-deciding factor in the therapeutic value of calcium in allergy. In fact, calcium gluconate may produce unfavorable results in the treatment of asthma, while calcium ascorbate may be useful.

Group 4.—Controls on this day showed fairly normal maintenance of the bronchiolar lumen, as well as a prompt response to a second dose of histamine hydrochloride after twenty-seven minutes.

Experiments 3 and 4: The histamine antagonism of benzedrine ascorbate was followed by active dilatation of the bronchiole. That this dilatation was active was demonstrated by a secondary response to histamine, although the secondary contraction brought the lumen to only a little below normal, and well above the initial histamine contraction.

Experiments 5 and 6: These tests were all the more interesting because benzedrine sulfate gave no such response as did benzedrine ascorbate; in fact, it prolonged histamine contraction and produced virtually no histamine block. Benzedrine sulfate may be considered as bronchiole constricting.

SUMMARY

In this group of experiments a remarkable difference in pharmacologic action is evident. While benzedrine ascorbate produced a quick recovery from histamine contraction, with strong histamine block, the benzedrine sulfate showed no histamine antagonism, and in fact prolonged histamine contraction. The implications of this experiment may be important in relation to histamine shock. While benzedrine sulfate can keep a soldier alert, it may predispose him to greater histamine shock, whereas the vitamin C salt may protect against histamine shock.

Group 5.—Experiments 1 and 2: The bronchiole used in these controls was sensitive and reacted strongly to histamine, with poor spontaneous recovery; after twenty-one minutes the bronchiole responded with sharp contraction to histamine. The spontaneous recovery from histamine was only about 44 per cent.

Experiments 3 and 4: Epinephrine ascorbate produced immediate recovery from histamine, with such strong histamine antagonism that the second dose of histamine hydrochloride did not prevent continuation of the bronchiolar dilatation to over twice the normal size.

Experiments 5 and 6: Epinephrine hydrochloride, as was to be expected, produced active recovery from histamine contraction, with moderate dilatation of the bronchiole.

Summary: One is struck by the remarkable synergistic effect of vitamin C on epinephrine. The epinephrine ascorbate showed about twice the bronchiole-dilating capacity exerted by epinephrine hydrochloride and a much quicker and more active histamine antagonism.

CONCLUSIONS

As a result of these studies several broad conclusions can be arrived at.

First, vitamin C plays a valuable role in the treatment of nasal allergy, but is useful fundamentally in large doses ranging from a minimum of 250 mg. daily with an optimum dosage of 750 mg. daily.

Second, that vitamin C is useful in allergy either by oral therapy or by injection.

Third, the results of the administration of vitamin C are in general advantageous to allergic patients with or without desensitization.

Fourth, in some cases vitamin C therapy alone proved superior to pollen desensitization in previous years.

Fifth, allergic disturbances are related to nutritional deficiencies, primarily that of ascorbic acid.

BIBLIOGRAPHY

1. Abbasy, M. A.; Harris, L. J., and Ellman, P.: Excretion of Vitamin C in Pulmonary Tuberculosis and in Rheumatoid Arthritis, *Lancet* 2:181, 1937.
2. Abt, Arthur F.: The Detoxifying Action of Vitamin C (Ascorbic Acid) in Arsenical Therapy, *J. A. M. A.*, 1692 Nov. 15, 1941.
3. Archer, H. E. and Graham, G.: On the Excretion of Ascorbic Acid, *Lancet* 1:710, 1936; Subcurvy State in Relation to Gastric and Duodenal Ulcer, *Ibid.* 20:364, 1936.
4. Aron, Hans, C. S.: The Detoxifying Action of Vitamin C (Ascorbic Acid) in Arsenical Therapy, *J. A. M. A.*, 1692, Nov. 15, 1941.
5. Barlow, O. W.; Beams, A. J.: A Comparison of the Bronchodilating Action of Several Anti-Asthmatic Agents After Anaphylaxis and Histamine Shock in The Guinea Pig, *J. Pharmacol. & Exper. Therap.* 47:111, 1933.
6. Biss, E.: Grave Erythroderma Due to Arsphenamine; Cases Cured by Cevitamic Acid, *Rec. med. de la Suisse Rom.*, 58:603, 1938.
7. Bourne, G.: The Effect of Ascorbic Acid (Vitamin C), Calcium Ascorbate, and Calcium Gluconate on the Regeneration of Bone in Rats, *Quart. J. Exper. Physiol.* 31:319, 1942.
8. Bundesen, Herman N.: The Detoxifying Action of Vitamin C (Ascorbic Acid) in Arsenical Therapy, *J. A. M. A.* 1692, Nov. 15, 1941.
9. Cameron, W. M.; Tainer, M. L.: Comparative Actions of Sympathomimetic Compounds: Broncho-Dilator Actions in Bronchial Spasm Induced by Histamine, *J. Pharmacol. & Exper. Therap.* 57:152, 1926.
10. Cormia, F. E.: Postarsphenamine Dermatitis: The Relation of Vitamin C to the Production of Arsphenamine Sensitiveness, and Its Use as an Adjuvant to Further Arsphenamine Therapy in Patients with Cutaneous Hypersensitivity to the Arsphenamines, *J. Invest. Dermat.*, 4:81-93, 1941.
11. Co Tui; Burststein, C. L.; Wright, A. M.: The Effect of Sympathectomy on the Sensitivity to Adrenalin of the Bronchioles, *J. Pharmacol. & Exper. Therap.* 58:33, 1936.
12. Dainow, J.: Considerations sur la pathogenie de L'erythrodermie arsenobenzolique: Role de la vitamine C Ann. de dermat. et syph., 10: 139, 1939.
13. Dainow, J.: Use in Reduction of Intolerance in Arsphenamine Used in Therapy of Syphilis: Relations to Avitaminosis to Intolerance Cases, *Presse Med.*, 45:1670-1672, Nov. 24, 1937.
14. Diaconescu, N., Constantinescu, V., and others: Vitamin C in Therapy of Arsphenamine Intolerance, *Rev. san mil.* Bucuresti, 37:627-630, 1938.
15. Falconer, E. H., Epstein, N. N. and Milk, Edith S.: Purpura Hemorrhagic Due to Arsphenamines: Sensitivity in Patients as Influenced by Vitamin C Therapy, *Arch. Int. Med.*, 66:319, Aug. 1940.
16. Farmer, Chester J.: The Detoxifying Action of Vitamin C (Ascorbic Acid) in Arsenical Therapy, *J. A. M. A.*, 1692, Nov. 15, 1941.
17. Greenbaum, Regina S.: The Detoxifying Action of Vitamin C (Ascorbic Acid) in Arsenical Therapy, *J. A. M. A.*, 1692, Nov. 15, 1941.
18. Harde, E.; Rothstein, I. A., and Ratish, H. D.: Urinary Excretion of Vitamin C in Pneumonia, *Proc. Soc. Exper. Biol. & Med.* 32:1088, 1935.
19. Holman, E.: Vitamin and Protein Factors in Preoperative and Postoperative Care of the Surgical Patient, *Surg., Gynec. & Obst.* 70:261, 1940.
20. Hunt, A. H.: The Role of Vitamin C in Wound Healing, *Brit. J. Surg.* 28:436, 1941.
21. Ingalls, T. H., and Warren, H. A.: Asymptomatic Scurvy, *New England J. Med.* 217:443, 1937.
22. Jackson, D. E.: The Peripheral Action of Certain Drugs with Special Reference to the Lungs, *J. Pharmacol. & Exper. Therap.* 4:291, 1913.
23. Jonnard, R. t Ruskin, S. L.: Etude Physico-Chimique Comparée du Gluconate, du Cevitamate de calcium et de la Vitamine C. Submitted C. R. Soc. de Biologie, Paris, Reb., 1938.
24. Jonnard, R. and Ruskin, S. L.: Etude physico-comparée du gluconate, du sel de calcium de la vitamine C et la vitamine C. *Compt. rend. Soc. de biol.* 28:266, 1938.
25. King, C. G.: Vitamin C, Ascorbic Acid, *Physiol. Rev.* 16:238, 1936.
26. Lanman, T. H., and Ingalls, T. H.: Vitamin C Deficiency and Wound Healing, *Ann. Surg.* 105:616, 1937.
27. Lauber, H. J.: Vitamins and Healing of Wounds and Burns, *Blatt. z. klin. Chir.* 158:293, 1933.
28. Lund, C. C.: The Effect of Surgical Operations on the Level of Cevitamic Acid in the Blood Plasma, *New England J. Med.* 221:123, 1939.
29. Macht, D. I.; Ting, G. C.: Response to Drugs of Excised Bronchi from Normal and Diseased Animals, *J. Pharmacol. & Exper. Therap.* 18:111, 1921.
30. Macklin, C. C.: Musculature of Bronchi and Lungs, *Physiol. Rev.* 9:1, 1929.
31. Moon, Virgil H.: The Vascular and Cellular Dynamics of Shock, *Monograph Blood Substitute and Blood Transfusion*, Stuart Mudd and Wm. Thalheimer, Charles C. Thomas, Publisher, 1942.
32. Ruskin, S. L.: The Influence of Vitamin C on Wassermann Fastness in Syphilis, *Am. J. Digest. Dis.* 10:170, 1943.
33. Ruskin, S. L.: Studies on the Parallel Action of Vitamin C and Calcium, *Am. J. Digest. Dis.* 5:403, 1938.
34. Ruskin, S. L. and Silberstein, M.: The Influence of Vitamin C on the Therapeutic Activity of Bismuth, Antimony and the Arsenic Group of Metals, *Med. Rec.* 153:327, 1941.
35. Ruskin, S. L. and Jonnard, R.: Studies in Calcium Metabolism: Further Contributions to the Comparative Studies of the Physico-Chemical Properties of the Gluconate and Cevitamate of Calcium and of Vitamin C. Reprint *Am. J. Dig. Dis.*, Vol. V—No. 10, pp. 676-680, Dec.
36. Sollman, T.: Gilbert, A. J.: Microscopic Observations of Bronchiolar Reactions, *J. Pharmacol. & Exper. Therap.* 61:272, 1937.
37. Sollman, T. A. *Manual of Pharmacology*, W. B. Saunders Co., 1943.
38. Sulzberger, M. G. and Oser, B.: Influence of Ascorbic Acid in Diet — On Sensitization of Guinea Pigs to Neotarsphenamine, *Proc. Soc. Expt. Biol. Med.* 34:716-719, 1934.
39. Tissel, M., and Harvey, S. C.: The Effect of Absolute and Partial Vitamin C Deficiency on Healing of Wounds, *Proc. Soc. Expt. Biol. & Med.* 38:518, 1938.
40. vonjeney, A., and Toro, I.: The Effect of Ascorbic Acid on the Formation of Fibers in Fibroblast Cultures, *Virchows Arch. f. path. Anat.* 298:87, 1936.
41. Wolbach, S. B., and Howe, P. R.: Intercellular Substances in Experimental Scorbutus, *Arch. Path.* 1: 1-24 (Jan.) 1926.
42. Went, A.; Martin, J.: Serum Sensitization, *Arch. Exper. Path.* in *Pharmacol.* 193:303, 1939.
43. Youmans, J. B.; Corlette, M. B.; Akeroyd, J. H., and Frank, H.: Studies of Vitamin C excretion and Saturation, *Am. J. M. Sc.* 191:319, 1936.
44. Cannon and Britton, *American J. of Physiol.* 1927.
45. Crane, M. M.; Woods, P. W.; Waters, E. M., and Murphy, E. F., *J. Nutrition*, 19, 16, 1940.
46. Minot, A. S.; Dodd, K.; Keller, M.; and Frank, H., *J. Pediat.* 16, 717, 1940.
47. Mouriquand, S., and Edel V., *Presse Med.* 51:353-4, 1943; *Chem. Zeit.* 1943, II, 1476.
48. Ruskin, S. L.: Influence of Vitamin C on the Anti-Histamine Action of Various Drugs, *Arch. of Otolaryng.* 36:853-873, 1942.

49. Ruskin, S. L.: Contribution to Study of Grippe Otitis, Myringitis Bullosa Hemorrhagica and Its Relationship to Latent Scurvy, *Laryngoscope* 48:327, 1938.
50. Ruskin, S. L.: Vitamin C-Sulfonamide Compounds In The Healing of Wounds, *Arch. of Otolaryngology*, 40:115-122, 1944.
51. Ruskin, S. L.: The Therapeutic Use of the Amino Acid Histidine in Allergy and Shock — "Histidine as a Factor in Histamine Epinephrine Balance", *J. Dig. Disc.*, II No. 7, July 1944.
52. Youmans, J. B.: Proceedings of the Eighteenth Annual Conference of the Milbank Memorial Fund, Milbank Memorial Fund, 1940.
53. Hamil, B. M.; Reynolds, C.; Poole, M. W., and Macy, I. G., *Am. J. Diseases of Child.*, 56, 561, 1938.
54. Marchmont-Robinson, S. W., *J. Lab. & Clin. Med.* 26: 1478-81, 1941.
55. Laundau, S. W., and Gay, L. N.: Influence of Certain Amino Acids on Histamine Reactions and Anaphylactic Reactions in Intestinal Strips of Guinea Pigs and in Intact Guinea Pigs; *Bulletin of The Johns Hopkins Hospital* Vo. 74 No. 1:55-76, January 1944.

Globin Insulin: A Clinical Study

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EVERY clinician who treats diabetic patients is confronted with the problem of stabilization of that metabolic disorder either by diet alone or with the assistance of insulin. When insulin becomes necessary, it is for obvious reasons, to the advantage of the patient to have as few injections per day as possible. From this point of view regular insulin and crystalline insulin have been found wanting. When Hagedorn and his associates introduced protamine insulin, which was later modified by Scott and Fisher by the addition of zinc to be known as "Protamine Zinc Insulin", it was thought that the answer to "one daily dose" of insulin was finally found. However, as clinical experience with this form of insulin accumulated it became evident that there are a number of patients who require the addition of regular insulin for proper stabilization. It was also found that, due to the precipitating effect of the excess protamine in protamine zinc insulin, both forms of insulin could not be introduced in the same syringe, but had to be administered separately. Recently attempts to use mixtures of protamine zinc insulin and regular insulin have been reported, either by means of specially prepared mixtures, (1, 2, 3), or by any graded extemporaneous mixtures. These methods have not won wide acceptance, being viewed as too complicated.

Within the past five years a number of reports on globin insulin have appeared in the American Literature (6, 7, 8, 9, 10). They are almost unanimous in their praise of globin insulin as superior to protamine zinc insulin. Its merit according to these investigators consists in the following:

1. Globin insulin will control practically all diabetics with one daily injection.

2. Globin insulin has a greater effect, unit for unit, than protamine zinc insulin. Hence, smaller doses of insulin are required.

3. Since the maximum effect of globin insulin is reached within 12 hours, hypoglycemic reactions, if they occur, will take place in the early evening, rather than during the night as with protamine; therefore they can be better controlled.

4. No allergic reactions occur with globin.

We became interested in globin insulin especially because of difficulties encountered with some diabetic patients treated in our Out-Patient Department with protamine zinc insulin. We therefore decided to hospitalize these patients and undertake a study of them, as well as of other severe diabetics admitted to Medical Ward, in order to compare the clinical effects of protamine zinc insulin and globin insulin. Particularly we wished to discover whether patients requiring separate injections of both protamine and standard insulin could be controlled with one dose of globin insulin.

PROCEDURE

Our plan was to give the patients a diet of caloric value suitable to their state of nutrition, with the carbohydrate content divided into 2/10 at breakfast, 2/10 at lunch and 6/10 at dinner. They were then stabilized with protamine zinc insulin alone or with a supplementary dose of regular insulin if necessary. Following this the diet was readjusted so as to give the maximum carbohydrate content during the noon meal, e.g. 2/10, 5/10, 3/10. Then globin insulin, usually 2/3 of the protamine zinc insulin requirement, was administered and stabilization attempted.

RESULTS

16 patients were studied, 5 of whom had previously been treated in our Diabetic Out-Patient Department. Table 1 shows the results in 10 patients of the group who were regulated satisfactorily with protamine zinc insulin alone. 6 of these required from 5-30 units less of globin insulin than of protamine zinc insulin to

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† The globin insulin used in this study was furnished by Burroughs Wellcome Co. U. S. A.

TABLE 1

Effect of Globin in Cases Requiring Protamine Alone for Stabilization

Case No.	Pt.	Sex	Age	Date 1944	Diet			Distribution of Carbohydrate	Insulin	Blood Sugars		
					P.	C.	F.			9 A.M.	4 P.M.	9 P.M.
*#1	J.B.	F	30	4/3 4/14	70 " "	150 " "	70 " "	2 - 2 - 6 2 - 6 - 2	50 P 50 G	102 109	212 115	255 100
*#2	S.G.	F	56	5/5 5/10	70 "	150 " "	35 " "	2 - 2 - 6 2 - 5 - 3	90 P 60 G	135 140	150 150	162
*#3	E.F.	F	58	5/11	75	150	35	2 - 5 - 3	55 G	133	126	—
					<i>Uncontrolled Prep. on 60-70 P. in O.P.D.</i>							
#4	J.B.	F	53	5/11 5/28 5/28	70 " " " "	150 " " " "	40 " " " "	2 - 2 - 6 3 - 4 - 3 3 - 4 - 3	25 P 25 G 25 G	149 162 155	105 92 —	130 194
#5	L.V.	F	59	5/23 6/3	60	150	50	3 - 3 - 3 - 1 2 - 5 - 3	50 P 45 G	126 152	161 162	— 70
*#6	E.C.	F	70	5/18 6/26	55 " "	150 " "	50 " "	2 - 2 - 6 2 - 5 - 3	40 P 30 G	102 115	125 152	— 154
#7	G.E.	M	65	6/24 7/13 7/14	60 " " " "	140 " " " "	50 " " " "	2 - 2 - 6 2 - 5 - 3	25 P 25 G 25 G	119 157 113	123 161 —	— — —
#8	L.S.	F	45	7/10 7/26	70 " "	150 " "	50 " "	2 - 2 - 6 2 - 5 - 3	25 P 25 G	141 150	108 142	— —
*#9	H.S.	M	69	7/17 7/24	70 " "	175 " "	50 " "	2 - 2 - 6 2 - 5 - 3	40 P 35 G	140 141	143 141	— —
#10	C.W.	F	49	8/15 8/22	70 " "	100 " "	30 " "	2 - 2 - 6 2 - 5 - 3	45 P 35 G	145 144	105 —	— 171

TABLE 2

Effect of Globin in Cases Requiring Protamine and Regular for Stabilization

Case No.	Pt.	Sex	Age	Date 1944	Diet			Distribution of Carbohydrate	Insulin	Blood Sugars		
					P.	C.	F.			9 A.M.	4 P.M.	9 P.M.
#11	M.S.	F	18	3/1 3/14	100 " "	225 " "	100 " "	2 - 2 - 6 2 - 5 - 3	60 P 80 G	125 223	149 199	— 318
#12	D.L.	F	45	3/31 4/1 4/13 4/14	70 " " " " " "	150 " " " " " "	70 " " " " " "	2 - 2 - 6 2 - 5 - 3	60 P 35 R 35 R 90 G 100 G 30 P	9 A.M. 6 P.M. 6 P.M. 108 187 108 172	108 — 182 224 195	175 — 210 — 203
#13	R.B.	F	63	5/25 6/8	75	150	50	2 - 2 - 6 3 - 4 - 3	50 P 10 R 50 G	120 — 156	175 — 119	— — 110
#14	A.M.	F	57	7/15 7/25	60	150	40	2 - 2 - 6 2 - 5 - 3	25 P 15 R 40 G	150 — 121	187 — 140	— — —
#15	R.S.	F	65	8/15 8/24	80	160	40	2 - 2 - 6 2 - 5 - 3	40 P 20 R 40 G	101 — 140	95 — 214	— — —
#16	O.D.	F	66	9/2 9/11	60	150	50	2 - 2 - 6 2 - 5 - 3	15 P 15 R 25 G 15 R	100 — 126	154 — 101	— — —

achieve the same degree of control. The other patients of this group needed the same dosage of either type of insulin for stabilization.

The results with the remaining 6 patients who needed separate injections of protamine and regular insulin to secure proper regulation are shown in Table 2. Only 2 patients, No. 13 and No. 14, were well stabilized with globin insulin alone. Case No. 15 achieved fair control with globin, but not so good as with protamine and regular insulin. The other 3 cases, 11, 12 and 16, could not be stabilized satisfactorily with one dose of globin insulin.

3 patients, cases No. 2, 11, and 12, complained of severe burning pain at site of injection of globin insulin. This was not serious enough to cause discontinuance of globin therapy. Martin, Simonsen and Homann (11) also have reported similar complaints by patients receiving globin insulin. 5 patients (cases 2, 3, 6, 8, 9) were subsequently followed up in the Out-Patient Department. One of these (case 3) who was well controlled on globin in hospital, did not continue this improvement in the Out-Patient Department, due to failure to adhere to diet. The remaining 4 cases followed the same course in clinic as in hospital.

DISCUSSION

The analysis of our results confirms the favorable reports of previous investigators on the value of globin insulin in moderately severe diabetics requiring a large dose of protamine zinc insulin alone for stabilization. However, in the more severe cases needing separate injections of protamine and regular insulin, our results with globin insulin were not so favorable. Only 2 of 6 such patients were controlled satisfactorily with a single dose of globin insulin.

REFERENCES

- Ulrich, H.: Clinical Experiments with Mixtures of Standard and Protamine Zinc Insulins, *Ann. Int. Med.* 14: 1166, 1941.
- Colwell, A. R. and Izzo, J. L.: Protamine Zinc Insulin Modified for Accelerated Action, *J. A. M. A.* 122: 1231 (Aug. 28) 1943.
- McBryde, C. M. and Roberts, H. K.: "Three to One" Modified Protamine Zinc Insulin, *J. A. M. A.* 121: 1243 (April 10) 1943.
- Peck, F. B.: Approximate Insulin Content of Extemporaneous Mixtures of Insulin and Protamine Zinc Insulin, *Ann. Int. Med.* 18: 177, 1943.
- Sparks, M. I. and John, H. J.: The Clinical Use of Mixtures of Insulins, *Ohio State M. J.* 39: 226, 1943.
- Bauman, L.: Clinical Experience with Globin Insulin, *Am. J. Med. Sci.* 198: 475, 1939.
- Bauman, L.: Further Experience with Globin Insulin, *Ibid.* 200: 299, 1940.
- Duncan, G. G., and Barnes, C. G.: The Action of Globin Insulin Compared with that of Crystalline, Unmodified, and Protamine Zinc Insulin, *Ibid.* 202: 553, 1941.
- Levitt, A. and Schaus, J. P.: Clinical Experience with Globin Insulin, *Med. Times* 70: 187, 1942.
- Paul, J. D., Globin Insulin, *Med. World*, 61: 443, 1943.
- Martin, H. E., Simonsen, D. G., & Homann, N. H.: Time Activity Curves of Globin Insulin with Clinical Applications, *Am. J. Med. Sciences*. Sept. 1944, Vol. 208, No. 3: 321-333.
- Mosenthal, H.: Globin Insulin with Zinc in the Treatment of Diabetes Mellitus, *J. A. M. A.* 125: 483 (June 17) 1944.
- Clinical Diabetes Mellitus & Hyperinsulinism—Russell M. Wilder-W. B. Saunders Co. P. 94-95, 1940.
- Sindoni, A., Jr.: Blood Sugar Versus Urine Sugar in Patients Treated with Prot. Zinc Insulin, *J. A. M. A.* 112, 2503: 2595 June 1939.

Close scrutiny of the literature on globin insulin reveals that there are few detailed clinical reports on any large series of cases which previously needed both protamine and regular insulin. In those papers, such as Mosenthal's (12), which do discuss this type of diabetic, the degree of regulation is judged by absence of glycosuria, rather than by blood sugar tests. Since in treatment with protamine zinc insulin it is often considered not advisable to eliminate glycosuria because of the danger of nocturnal hypoglycemia (13); and further because of the well known wide individual variations in renal threshold for glycosuria (14), it is clear that there are many pitfalls in evaluating diabetic control by urinary sugars alone.

CONCLUSION

Globin insulin is as good or better than protamine zinc insulin in the moderately severe diabetic, requiring one large dose of protamine zinc insulin for proper regulation. It may be of advantage in those cases exhibiting allergic reactions to protamine and in those subject to nocturnal hypoglycemia. Globin insulin did not show such uniformly good results, in our hands, in the more severe diabetics, in whom separate injections of protamine and regular insulin are necessary. However, it is worth a trial in such patients, in the attempt to eliminate extra injections of insulin.

SUMMARY

- Six of ten patients required less globin than protamine for satisfactory diabetic control. The other four cases were regulated with the same dose of both types of insulin.
- Of six patients stabilized with protamine and regular insulin, only two were able to secure similar regulation with globin insulin alone.

Pyogenic Infections of the Perineum and Buttock Skin

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CHICAGO, ILL.

THE management of all staphylococcal infections of the perianal and buttock skin follows the same general principles regardless of their severity. Boils usually begin as single foci of infection but by autoinfection lead to a series of eruptions. Our first effort is to keep the skin dry and sterile.

Prevention:

1. After each defecation the entire buttock should be wiped with a weak solution of ethyl alcohol.
2. Each evening a warm epsom salts sitz bath for 15 minutes mechanically cleanses the whole area.
3. After the bath the entire area should be wiped with 1:5,000 bichloride solution.

Palliation:

If an infection has definitely developed, and especially if a crop of boils is present the patient's activities should be restricted. Hot sitz baths two or three times daily are very comforting. In the morning when the individual must go about his duties a dusting powder of sulphur and at night a careful application of Ammoniated Mercury ointment 5 per cent or painting the entire surface with 10 per cent mercuriochrome is usually efficient. When suppuration has occurred, and the boil "points", but not otherwise, the pustule may be carefully nicked with the point of a sterile scalpel, its contents evacuated and its base cauterized. Trauma should be avoided. Squeezing the lesion to assist the escape of material invariably increases the inflammatory process. Multiple and recurrent infections are benefited by a course of X-ray or ultra-violet therapy.

Penicillin:

The effectiveness of penicillin in the treatment of staphylococcal infections is at present only under clinical study but much data is being accumulated rapidly. The sodium salt is used and may be administered intravenously or intramuscularly or applied topically. Not all staphylococcal lesions respond to penicillin and failure of the mold to act is thought to be due to an enzyme named penicillinase which may be produced by certain bacteria and is responsible for the destruction of the bacteriostatic property of penicillin. Bacteria producing penicillinase include gram-negative bacilli normally found in the intestine and which may prevent activity of penicillin against suppurative infections within the rectum and upon the anal and buttock skin. Penicillin is unable to penetrate necrotic tissue or walled-off abscesses and is inactivated by gastric and pancreatic juices.

With so potent a preparation as penicillin it is but logical to presume that there may be serious reactions in either unusually sensitive individuals or to as yet unknown ferment and chemicals in the penicillin. The reactions more frequently reported are thrombophlebitis, urticaria, chills with or without fever after the intravenous injection, faintness and flushing of the

face. Reactions reported so far that have apparently been derived from the intravenous injection of penicillin have been of two types, mild sensory changes, and severe sensory and motor changes. Both types of lesions have involved the lower segments of the spinal cord or the roots of the lumbosacral plexuses of nerves. The mild sensory changes consisted of pain in the legs and pain in the back; during the intravenous administration of the penicillin. These symptoms persisted until the penicillin dosage was reduced or discontinued and then disappeared. The severe reactions included sharp pain in the legs and toes, and hypotonic neurogenic bladder with urinary retention and overflow. Also there was paralysis of both legs with pronounced hyperesthesia and absent tendon reflexes.

In the carbuncle case here reported one ampule of dry penicillin (100,000 units) was dissolved in 2,000 cc of sterile saline solution. This made a strength of 50 units per cc. of solution and was given as an intravenous drip at the rate of 30 to 40 drops per minute. On the second day another ampule (100,000 units) was dissolved in 2,000 cc. of 5 per cent glucose solution. On the third day the penicillin was dissolved in normal saline solution. By this time his temperature was falling, the cellulitis was receding and the intravenous drip was discontinued and replaced with wet dressings of penicillin in 250 units per cc. of saline solution administered through rubber tubes. When granulation seemed well established the wet dressings were discontinued and an ointment of penicillin 300 units per cc. of base was applied and changed three times daily.

When can the penicillin be discontinued with safety is a question that at present cannot be definitely answered. Patients who have been fever free for as long as four days have shown a recurrence of the infection when the penicillin was reduced. Therefore we continued penicillin for seven days after the clinical evidence of infection had subsided.

Staphylococcus vaccines:

In the furunculosis patient we gave a course of staphylococcal toxoid subcutaneous injections beginning with 0.1 cc. of the undiluted toxoid and doubling the dose each succeeding dose, given at 3 day intervals until 1 cc. of the undiluted toxoid was given. In another patient with furunculosis we used staphylococcus bacteriophage injections. The action of both of these preparations is slow and we are not able to determine their therapeutic value.

Constitutional therapy:

In a prolonged seizure of furunculosis the general health becomes impaired and the anemia should be anticipated by a diet high in calories, vitamins and minerals. A generous diet which includes milk one quart, cream 3 ounces, 2 eggs, one half pound of red meat, fish or liver, and three tablespoonsfuls of green vegetables per day will be of much service. Reduction of the carbohydrates in the diet has usually been

recommended and yet Tauber (1) obtained good results by the intravenous injections of dextrose combined with a high carbohydrate diet. The two elements calcium and phosphorus are necessary in life processes. They are the most important constituents of the skeletal system and play an important role in the regulation of nervous, muscular, and glandular activity, and in the maintenance of neutrality in the organism. Calcium and phosphorus exert a definite effect on each other and a deficiency of one will retard metabolism of the other, while a proper balance aids their utilization and that of iron and other minerals. Vitamin B in the form of Brewers yeast tablets, or thiamine chloride is said to relieve the fatigue and physical exhaustion but are of doubtful service.

Case Reports—

Essential Pruritus Ani: P. S., age 52, clergyman has had periodic anal pruritus associated with excessive secretions from the skin and sweating about the perineum. The anus is always wet and the skin is soggy, thickened and excoriated. He has had several types of treatment without relief. Penicillin was suggested rather empirically although the possibility of the streptococcus fecalis being a complicating organism was kept in mind. He was hospitalized, given 100,000 units of the sodium salt of penicillin intravenously in 2,000 cc of saline solution and packs wet with penicillin 250 units per cc. of normal saline solution through rubber tubes were applied to the anus. The packs were removed only when he went to stool. The first night under treatment he slept the whole night through, a rest he had not had for several months. After the third day he was quite comfortable, and the perianal integument lost its soggy character. The penicillin was discontinued and a routine followup course conducted. He has been very comfortable since.

Furunculosis: T. McE—, age 24, physician. In the fall last year he noticed itching about the anus and later he developed a boil on his buttock. Later he had a siege of about 20 boils. He employed hot baths, scrupulous hygiene, and impercaine ointment with only temporary and partial relief. At that time

he entered the hospital, several of the furuncles were carefully opened and he received 800,000 units of penicillin intravenously. He rapidly recovered and went home in 7 days, but had to return within a week because other furuncles appeared. Given another course of 800,000 units he had an equally prompt relief and since then he takes a warm sitz bath each night and then wipes the buttocks gently with 1-5,000 bichloride solution. He has had no further furuncles.

Carbuncle:

Mr. M., age 50, office employee, was seen with a sloughing carbuncle of 5 days duration upon his right buttock. The cellulitis involved the anus and perineum. The carbuncle at this time was a sloughing crater and the cellulitis intense. He was rational but was suffering intensely and had a temperature of 103.2. He was given 100,000 units of penicillin intravenously every night and packs wet with penicillin were applied to the ulcer continuously. On the third day the sloughs separated and healthy granulations developed.

Para-anal abscess: H. P., butcher, had two large prolapsing venous hemorrhoids and two fistulas which opened externally on the right buttock and internally in the rectum at the level of the internal sphincter. The hemorrhoids and fistulas were excised and convalescence was uneventful except that there persisted an excess secretion of mucus from the anus which kept the parts moist. By careful hygiene he had no trouble for over a year and then an abscess developed in the right buttock two inches from the anus. It was treated conventionally until it opened and then he was given 20,000 units of penicillin intramuscularly at 10 a. m., 1 p. m., 4 p. m., 7 p. m. and 10 p. m. for 3 days. During that time the cellulitis subsided, the wound healed and he went his way.

Summary:

These patients are reported because of the dramatic relief afforded by penicillin supplementing otherwise well established procedures. Not all of our patients have responded so promptly.

1. Tauber, Hyperglycemia in diseases of the skin. *Arch. Derm. & Syph.* 27: 198, 1933.

Abstracts of Current Literature

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CLINICAL MEDICINE

STOMACH

HOWARD, J. T.: *Experiences with the gastroscope over a period of six years.* (*Southern Med. J.*, v. 38, p. 233, May, 1945.)

While gastroscopy enables us to visualize most gastric tumors and ulcers and to detect gastritis, the procedure on the whole is not as dependable as the X-ray. Gastroscopy reveals no tumor or ulcer that X-ray does not reveal. This opinion is based on experience gained

in the study of numerous cases, the case histories of which are included in the article. Howard believes that while chronic gastritis is an interesting finding, its importance is really small and that frequently symptoms are erroneously ascribed to it. The significance of this paper may be summed up thus: "gastroscopic demonstration of gross lesions is of the greatest importance, but a negative gastroscopic examination does not exclude the possibility of gastric ulceration or tumor."—F. X. Chockley.

COHEN, L. AND HARRISON, I.: *Gastric function in amoebic dysentery.* (*South African J. Med. Sci.*, v. 10, p. 27, Feb. 1945).

The presence of amoebae in the alimentary tract is not in itself responsible for the frank dysentery which is seen in many parasitized patients. Individuals may harbor the amoeba in their intestine without displaying any signs of dysentery. It has been suggested that in the production of dysentery in amoebiosis malnutrition may play an important role. Since it is believed that the hydrochloric acid in the stomach acts as an amoebicidal agent, this study on gastric secretion was undertaken. Neutral red excretion functions by the stomach were tested in 25 cases of clinical amoebiosis. No deviation from the normal was found. It is the authors' conclusion that hypoacidity in amoebiosis cases with malnutrition is not responsible for dysentery.—M. H. F. Friedman.

OLSEN, A. M.: *The value of gastroscopic examination in the diagnosis of gastric disease.* (*Staff Meet. Mayo Clinic*, v. 20, p. 55, Feb. 21, 1945.)

Conditions contraindicative to gastroscopic examination include marked obesity, severe cardiac or respiratory disease, esophageal lesions, and deformities of the vertebral column. In old patients and in those mentally unstable or very emotional there should be considerable discretion used before undertaking passage of the gastroscope. Gastroscopic examination should not be a routine procedure but one serving as an aid to other methods of diagnosis. Only when history, physical examination, and laboratory data fail to establish diagnosis should gastroscopy be used.

Complete visualization of the stomach is impossible because of features in the structure of the gastroscope. Most easily seen are lesions in the mid-portion of the stomach near the angle. Lesions near the cardiac orifice are not seen readily.

Gastroscopy is most commonly indicated when roentgenoscopic examination yields negative results and yet the clinical history is suggestive. Both the roentgenologist and gastroscopist should be extremely cautious in attempting to differentiate between benign and malignant ulcer of the stomach. The milder forms of gastritis show a mucosa which may appear to be normal and differentiation is difficult. Olsen believes that the greatest usefulness to which gastroscopy can be put is evaluation of post-operative syndromes. Gastritis or ulceration at the anastomotic junction can be shown.—I. M. Theone.

BOWEL

ETHERINGTON-WILSON, W.: *Torsion of the great omentum: report on four cases.* (*Proceed. Royal Soc. Med.*, v. 38, p. 185, March 1945).

The great omentum may twist as a whole or as a part. The twist may be primary and of unknown cause or it may be a secondary rotation due to hernia, adhesion, intra-peritoneal inflammation, etc. About 190 cases of all varieties have been reported in the past: 38 per cent of these may be classified as idiopathic. Too many cases in the literature have been mislabeled omental torsion when actually they are torsions of gastrocolic strips or tags. A separate group for torsion of the whole great omentum should be formed. Diagnosis is typical: complaints of right-sided pain which gradually increases and may be relieved by lying down. Altho tenderness, rigidity and distension are absent, eighty per cent of the cases have been misdiagnosed as appendicitis. The most logical procedure is explorative operation as soon as possible. The omentum or part of it should be removed. The removed omentum should be examined carefully for pedicle formation, fibrosis, tumor, etc.—F. E. St. George.

ELMAN, R. AND READ, J. A.: *Nutritional recovery following removal of all but three feet of jejunum and half of the colon.* (*J. Missouri State Med. Assoc.*, v. 42, p. 145, March, 1945).

The case history and report of two operations on a male, aged 32, are given. The patient had a draining fecal fistula and had undergone many operations for regional ileitis before the two operations reported here. On examination it was found that his urine contained fecal material. At operation it was found that the patient had only 3 feet of normal jejunum; this emerged from the ligament of Treitz. The remainder was a mass of matted, adherent intestine. In an attempt to mobilize more of the small intestine it was discovered that the entire remainder was ulcerated and diseased beyond recovery. An isoperistaltic side to side anastomosis was performed between the normal portion of the jejunum and the normal transverse colon. There was a large extra alimentary abscess in the pelvis and because of this the diseased intestine was not removed at this time. At the second operation, 9 days later, the jejunum was found to have hypertrophied to twice its previous size. The remaining colon and small intestine were excised and the mass of diseased intestine was removed in one piece. The urinary and lateral abscesses were drained and the operation completed. The patient's recovery was uneventful. Within 3 months he had gained 40 pounds on an unrestricted diet. It is believed that this swift return to normal was due to the fact that compensatory mechanisms had developed during the years in which more and more portions of the small intestine had been removed.—F. X. Chockley.

FINN, W. F. AND LORD, J. W.: *Carcinoma of the colon producing acute intestinal obstruction during pregnancy.* (*Surg. Gynecol. Obstet.*, v. 80, p. 545, May, 1945).

Carcinoma of the colon is probably one of the rarest complications of pregnancy. Several cases have been reported previously. This case of a woman who was 6 months pregnant, is interesting because the initial symptom was obstruction rather than dystocia or perforation. Therefore, none of the symptoms relative to the carcinoma could be compared with factors arising from the pregnancy. The authors stress the value of multiple stage operation and the importance of aseptic anastomosis. The patient is well three months post-partum.—E. Feaver.

SINCLAIR, J. G.: *Intestinal hernia with eversion and ectrophic bladder.* (*J. Pediat.*, v. 26, p. 78, Jan. 1945).

In a six and one-half pound premature infant there was a defect of the ventral wall extending from the umbilicus to the anus. The infant died at four months of dehydration and emaciation. The umbilical herniation protruded candidly thru the umbilical cord and tho small at first, it developed into a long tube. The head, chest, and upper abdomen were normal at autopsy. The vascular system was normal; the spleen showed slight blood destruction. Although the ureters opened directly to the body surface neither the ureters nor the kidneys were infected. The ileum, 56 inches long, passed into the hernial sac and was then everted; it showed mucosal structure with epithelium and transverse villi. With every peristaltic wave yellowish fecal material was pushed from the open end of the ileum. The anal pit opened into a 3-inch blind tube. The ovaries were developed normally. The defect was believed to have its origin in the first formation of the ventral wall and perineum. The yolk stalk did not separate from the genital sinus and allantois. The author expresses the belief that a genetic factor exerted a great influence in this and similar cases.—G. N. N. Smith.

MEOLA, F.: *Diarrhea of newborn.* (*Ohio State Med. J.*, v. 41, p. 137, Feb. 1945).

The course of an epidemic of infantile diarrhea in a hospital nursery is described. The onset apparently was sudden. The stools, which were yellowish or greenish and foul smelling, yielded no organism on culture which could be designated as the one responsible. Dehydration, loss in weight, acidosis, circulatory collapse, and mental symptoms were dominant symptoms in the more severe cases. Treatment consisted of combating the acidosis and restoring fluid balance by administration of saline, glucose, plasma, or whole blood. Fluids by mouth were given whenever possible.

Mortality was high, being 32 per cent among 34 affected infants. Sulfonamides were very beneficial and probably accounted for the greatest percentage of survival since those patients receiving just supportive measures alone did not do as well as those receiving sulfasuxidine. The author advocates wider use of the sulfonamides in infantile diarrhea and urges that treatment should be vigorous and prolonged.—H. Stilyung.

MAYENBURG, H. von.: *Pathologic anatomy and pathogenesis of regional ileitis.* (*Schweiz. Zeitschr.*,

Allg. Path. Bakter., v. 2, p. 217, 1939).

Ulcerating processes of different etiology permit the contact of the intestinal content with the deeper layers of the gut wall. The resulting chronic inflammation leads to the described picture of ileitis regionalis. A special constitutional factor, however, seems to be necessary for the development of this condition.—Courtesy Biological Abstract.

KUCHER, I. S.: *Peculiarities of the course of dysentery in children with alimentary dystrophy.* (*Pediatria*, v. 1944, p. 56, 1944).

This study was performed during the German siege of Leningrad, which caused a terrible famine among the citizens of the city and alimentary dystrophy among the children. An almost complete disappearance of measles, scarlet fever and cerebro-spinal meningitis was noted; at the same time the number of cases of whooping cough, chickenpox, diphtheria and dysentery increased considerably. One hundred and forty-four children admitted to the dysentery ward of the hospital between March 15th and Nov. 15, 1942 were studied. There were more males than females in this group, with the females showing a greater number of deaths. Due to starvation, most of the patients showed complete absence of subcutaneous fat; muscle atrophy, profound weakness cyanotic extremities, gray facies, and in some cases hunger edema. Avitaminosis C prevailed. No history could be obtained from the relatives dazed by hunger. Some of the patients exhibited an intense reaction to the infective agent of dysentery. The majority, however, had a decrease in reaction or no reaction at all with normal or subnormal temperature; a chronic course (up to 3 months duration), and appearance of dysenteric stools with longer periods of enterocolitic stool and insignificant intoxication. They had an unusually marked appetite, but eating caused them to vomit, to refuse food, and to become worse. Complications noted were: pneumonia in 60 per cent of the cases mostly symptomless with no general reaction to the infection, pyuria in 18 per cent, otitis in 3 per cent, myocarditis in 31 per cent. Treatment consisted of diet (at that time mostly unobtainable), heat and general care. Sulfonamides failed to improve the cases, which did not react to the infection. Blood transfusions were used. The highest mortality was seen in the month of March when of 13 patients admitted, 8 died, and during April when 24 of 33 died. After that time the food situation in Leningrad improved and the mortality rate decreased.—Courtesy Biological Abstract.

PANCREAS

ANDERSEN, D.: *Celiac syndrome.* (*Ain. J. Dis. Child.*, v. 69, p. 221, 1945).

Seventeen patients with pancreatic fibrosis were studied from the viewpoint of fecal fat. The amount and appearance of the stools were often normal up to six months except for the penetrating "stale marigold" odor. After the child was placed on solid foods the stools became large but were formed and of normal color and consistency. With a normal amount of in-

gested fat microscopic examination revealed an abnormal amount of fat. In pancreatic insufficiency the proportion of fat in dried feces was found to be greater under six months than in older children. Neutral fat was above normal limits in only 3 instances. Feeding of pancreatin lowered the total fecal weight and the amount of fat excreted. From experiments on varying the diets the author draws the following conclusions. The diet for the child with pancreatic insufficiency is the same as that for celiac disease except the carbohydrate should be cereal or potato starch, if chemically tolerated, rather than banana. Sucrose is tolerated in normal amounts. Protein should provide 25 per cent of the caloric intake. The fat level should be low. Pancreatin should be given and also supplemental vitamins A and D.—Wm. J. Snape.

ANDERSEN, D.: *Celiac Syndrome: The determination of fat in feces, the reliability of two chemical methods and a microscopic estimation. Excretion of feces and fecal fat in normal children.* (*Am. J. Dis. Child.*, v. 69, p. 141, 1945).

The proof of steatorrhea requires a quantitative method of analysis. The very existence of several accepted methods of determination of fecal fat is indication for the evaluation of the various methods. The Sperry method was found more reliable in the author's hands than that of Forweather. The latter method is criticized because of the technical difficulties inherent in it. The article gives mean figures for normal children for wet and dry weight of stool per day, total fat content, neutral fat and fatty acid content. It is interesting that these vary with age groups. Children under six months showed increased amounts of fats and a smaller proportion of neutral fat.

The significance of various fractions of fat must be interpreted in the light of the diet, medication, and the technique of collection. For example, patients with pancreatic insufficiency fed on low fat diets have a normal neutral fat excretion. The administration of mineral oil and other lubricants will enormously affect the volume of neutral fats. It is to be remembered that neutral fat is split in the colon by the normal bacterial flora whose activity may continue *in vitro* even at 4° C.

There is a gross correlation between fat determined by microscopic method and chemical methods for total fat in feces. This method is useful in screening out patients with steatorrhea.—Wm. J. Snape.

LIVER AND GALL BLADDER

MCAULIFFE, S. W., AND WAKEFIELD, H.: *Observations on the human electrocardiogram during experimental distension of the gall bladder.* (*J. Lab. Clin. Med.*, v. 30, p. 349, Apr., 1945).

The relationship between organic heart disease and biliary tract disease was studied in seven female patients, all of whom had gall stones. On all seven patients cholecystectomies were performed. Electrocardiograms, using Lead II most frequently, were taken pre-operatively, during administration of anesthesia, during the operations and post operatively. Morphine sulfate and atropine sulfate were administered preoperatively.

Normal salt solution was injected into the fundus of the gall bladder thru a fine hypodermic needle. During this distension either an increased or normal heart rate was noted; never a decreased heart rate. During distension there was often a partial block and after distension, extrasystoles were noted frequently. However, from their observations, the authors believe that it is not possible to predict the effect of distension of the gall bladder on the human electrocardiogram. A discussion of the paper is included in the report.—M. H. F. Friedman.

HOFFBAUER, F. W.: *A correlation of composite liver function studies with histologic changes in the liver as noted in biopsy material.* (*J. Lab. Clin. Med.*, v. 30, p. 381, Apr., 1945).

A liver function "profile" was obtained on 48 patients, and 53 needle biopsies were performed. Liver function tests performed on the non-jaundiced patient were quantitative fractional serum bilirubin, hippuric acid, fractional serum proteins, cephalin-cholesterol flocculation, bromsulfalein, and urine urobilinogen. On jaundiced patients, the above tests were done plus total serum cholesterol, serum phosphatase, Quick prothrombin time (before and after vitamin K) and feces urobilinogen. In cases where the results of these tests were doubtful more sensitive tests were carried out. Such complete liver function studies, it is believed, will add greatly to the understanding of the pathologic physiology of jaundice and liver disease, of the anatomic type of hepatic disease and of the prognosis.—R. L. Burdick.

DIXON, C. F. AND LICHTMAN, A. L.: *Congenital absence of the gall bladder.* (*Surgery*, v. 17, p. 11, Jan. 1945).

Since 1900 there have been reported 50 cases of congenital absence of the gall bladder. In addition ten cases have been found in the Mayo Clinic records. In more than half of the cases the symptoms presented were those seen in cholelithiasis. Almost half of the cases had jaundice and 27 per cent had stones in the common duct. In most of the patients over 45 years old symptoms were present. Prolonged drainage thru a T-tube is recommended in cases with symptoms.—B. R. Adolph, Jr.

WOOD, P.: *Erythrocyte sedimentation rate in infective hepatitis and in malaria.* (*Brit. Med. J.*, No. 1, p. 9, Jan. 6, 1945).

Differentiation of infective hepatitis in the early stages before the onset of jaundice from malarial infection is an important but frequently difficult diagnostic step. The present paper points out that the sedimentation rates in the two diseases are different. In infective hepatitis the sedimentation rate is normal during the first ten days and rises slowly only after biliuria is present. In contrast, in malaria the sedimentation rate during the first ten days is usually above 10 mm per hour and between the tenth and twentieth days it is usually from 11 to 53 mm per hour. Wood concludes that an erythrocyte sedimentation rate above 20 mm

per hour during the first week or ten days is strongly in favor against a diagnosis of infective hepatitis.—F. E. St. George.

HEATLEY, T. F. AND BASCOM, G. W.: *Foreign bodies in the gall bladder. Case report.* (*Ohio State Med. J.*, v. 41, p. 333, Apr. 1945).

Foreign bodies in the gall bladder are not common findings either at operation or in routine autopsies. The patient, a woman aged 61 years, swallowed a safety pin twenty years previously. She was also accustomed to holding straight pins in her mouth and may perhaps have swallowed one or more. An acute episode of left-sided pain, loss of appetite and of weight was diagnosed as gallstone. Subsequent to recovery from the acute attack X-ray revealed foreign metallic bodies in the gall bladder. At operation two pins (or parts of a safety pin?) were found in the gall bladder, these had perforated thru the bladder into the liver and fibroid adhesions fixed the gall bladder to the liver at the site of perforation. The patient recovered good health following the operation.—B. R. Adolph, Jr.

ULCER

LEWISOLIN, R.: *Gastric resection for duodenal ulcer.* (*Surg. Gynecol. Obstet.*, v. 80, p. 355, Apr., 1945).

Lewisolin states that hyperacidity and duodenal ulcer are closely interwoven. While gastric resection is superior to gastro-enterostomy, it does not cure every patient with duodenal ulcer. The patients not cured after a properly performed gastric resection number about 5 to 10 per cent. The gastric resections reported as being beneficial have been subjected to "partial gastrectomy" and "subtotal gastrectomy". According to Lewisolin the term "subtotal" is here misused since no gastric resection for duodenal ulcer reaches as far as the cardia. On the other hand, the resection for gastric ulcer may indeed be "subtotal."

Comparing statistics of results of operations performed at different hospitals by different surgeons is difficult and not always reliable. The mortality from gastroenterostomies and gastrectomies recorded by a particular hospital will depend largely on the operation which is featured at that hospital as the operation of choice since obviously the procedure which is used only occasionally will have a higher percentage of fatalities. On the whole, the mortality for gastrectomies, partial or subtotal, has decreased materially within the past 5 to 10 years. The mortality for resection should not be higher than for gastroenterostomy if the operation is done by experts.

A case should not be regarded as a "healed ulcer" unless the biopsy specimen of the ulcer area shows previous ulceration. It is fallacious to consider that ulcers vary in different countries as to the type of operation which would be most suitable. Ulcers are not "milder" in one country than in another.—M. H. F. Friedman.

THERAPEUTICS

GILLMAN, T., GILLMAN, J., INGLIS, J., FRIEDLANDER, L., AND HAMMAR, E.: *Substitution of whole stomach*

extract for vitamins in the treatment of malignant infantile pellagra. (*Nature (London)* v. 154, p. 210, 1944).

Vitamin therapy was without value in the treatment of pellagra in children suffering from acute malnutrition; stomach extract (ventriculin) effected a rapid alleviation of the pellagric symptoms.—Biological Abstract.

URBACH, ERICH, GEORGE JAGGARD, AND DAVID W. CRISMAN.: *The experimental approach to the oral treatment of food allergy.* (*Ann. Allergy*, v. 2, p. 424, 1944).

Food propeptans are food digests derived from individual foods by means of prolonged digestion with hydrochloric acid and pepsin followed by additional digestion with trypsin. The preparations contain no native protein, but consist of 80-85 per cent of type specific proteoses and peptones. The remainder of the material consists of subpeptides, simple peptides, and amino acids. When administered by the intravenous or oral route to highly sensitized guinea pigs, the animals are protected against 20 or more minimum lethal doses of the substances to which they are sensitive. The authors conclude that these experiments confirm the value of food propeptan, orally administered in the treatment of food allergy.—E. Urbach.

FRIDMAN, E. I.: *Some peculiarities in the pathogenesis and treatment of anemia in children with alimentary dystrophy.* (*Pediatria*, v. 1944, p. 23, 1944).

600 alimentary dystrophic children with anemia were found to be scorbutic; a similar number of children were rachitic; 7-8 definite cases of pellagra and one case of sprue occurred. Improvement of the diet and vitamin administration yielded good results in most of the cases. Blood transfusions were given to speedy recovery. Cases which did not respond to this treatment were seen to improve when thiamine chloride and niacin both were given. The anemias accordingly were believed to be caused both by the starvation diet and by multiple vitamin deficiency. There were, however, several cases among this series which failed to improve; especially among those exhibiting the symptom complex to Jakob-Hayem's anemia. In these cases recovery was achieved by the administration of purified solution of liver (campolon). In addition to multiple avitaminoisis, the absence of the antianemic principle of Castle in the food seemed to be an important factor in the pathogenesis of anemia in alimentary dystrophic children. Campolon appeared to influence the other symptoms of severe alimentary dystrophy. Four cases are reported and discussed. The literature is reviewed.—Courtesy Biological Abstract.

HANNO, H. A. AND MERSH, M.: *Eosinophilia following parenteral liver therapy.* (*Am. J. Med. Sci.*, v. 209, p. 572, May, 1945).

Eosinophilia occasionally develops in patients who have been receiving therapeutic liver and liver extracts.

It commonly develops after raw or poorly cooked liver has been administered repeatedly over a long period but occurs much less frequently as the result of parenteral liver extract administration. In the present case a marked eosinophilia followed parenteral liver therapy. There could be found no clinical manifestations of frank allergy and skin testing yielded negative results for the liver extract used.—I. M. Theone.

SURGERY

WAUGH, J. M. AND CUSTER, M. D.: *Segmental resection of lesions occurring in the left half of the colon with primary end-to-end aseptic anastomosis: report based on fifty cases.* (*Proceed. Staff Meet. Mayo Clinic*, v. 20, p. 124, Apr. 18, 1945).

Primary aseptic end-to-end anastomosis was performed in fifty consecutive cases subjected to resection for lesions of the left half of the colon. For lesions of the midsigmoid and above the operation is a safe one-stage procedure with possible curative end results. Convalescence is rarely longer than three weeks. For lesions in the lower sigmoid and upper rectum this operation makes possible the retention of the sphincter ani. Convalescence averages about one month.

In the 50 cases there were only two deaths. This low mortality is attributable to the use of succinylsulfathiazole in preparing the patient and to the one-stage operation. Proximal colostomy is usually unnecessary for lesions higher than the midsigmoid or in the mid-sigmoid. Proximal colostomy is indicated when the lower sigmoid region is removed.—D. A. Wocker.

DONSON, J. H.: *Postoperative hemorrhage in anorectal surgery.* (*Southern Med. J.*, v. 38, p. 352, May, 1945).

Post operative hemorrhage following anorectal surgery may be either intermediate, occurring within 24 hours after operation, or secondary, taking place 24 hours to several days after operation. Intermediate hemorrhage is chiefly due to mechanical or physical factors, such as cutting ligatures, poorly applied dressings, inadequate control of bleeding, etc. Certain blood diseases such as leukemia or hemophilia are of course also contributory. Secondary hemorrhage, occurring most commonly about the seventh to tenth day, is nearly always due to infection and sloughing in the operative field.

The symptoms of post operative hemorrhage vary; the most serious problems were in cases of internal bleeding. The onset may be insidious and without outward signs, to be followed by a sudden spouting of blood, serious enough to endanger the patient's life. It must be remembered that blood in the stool is not necessarily from the rectum. Indeed, the whole colon may be filled with blood before any evaenation takes place. Once the hemorrhage has been corrected, recurrence is possible but in the author's cases this has not taken place. Furthermore, he has no record of a hemorrhage having been fatal.—F. X. Chockley.

METHENY, D. AND OLSON, H. H.: *An appendectomy on a poliomyelitis patient in a Drinker respirator.* (*Western J. Surg. Obstet. Gynecol.*, v. 53, p. 88, March, 1945).

The Drinker respirator, or so-called "iron lung", has been in use since 1929. During the intervening years numerous patients confined within the apparatus have had need of surgery for various conditions. The present is believed the first report of surgery for appendicitis in a patient with complete paralysis of the respiratory muscles. The anesthetic was nitrous oxide with a small amount of ether and was administered by positive pressure. When properly prepared the patient was removed from the respirator for a period of 15 minutes. During this period of operation artificial respiration was administered by alternate pressure on the chest and on the rebreathing bag of the gas machine. Recovery was uneventful.—M. H. F. Friedman.

SAINT, J. H.: *On the use of the vitallium tube in stricture of the common bile duct.* (*Western J. Surg. Gynecol. Obstet.*, v. 53, p. 73, March, 1945).

Vitallium is a dental alloy composed of cobalt, chromium and molybdenum and is devoid of electrolytic action. Its inertness makes it useful where contact with tissue or body fluids for any length of time is necessary. A vitallium tube to keep open a constricted common bile duct was first used in 1940. More cases have been recorded to date but the total number still remains too small to permit proper evaluation of the treatment. The present case is one in which the tube was used on a stricture operated on for the first time. This is in contrast with the cases previously reported in which the vitallium tube was resorted to only after other measures had proved unsuccessful. The patient here described made satisfactory recovery and was still in good health nineteen months after operation. The author notes the existence of records of cases in which no symptoms following use of the tube have been noted for several years. The degree of success in the use of the tube is considerable and the encouraging results certainly warrant further studies.—M. H. F. Friedman.

ETHERINGTON-WILSON, W.: *Appendicitis in the newborn: report on case 16 days old.* (*Proceed. Royal Soc. Med.*, v. 38, p. 186, March 1945).

Acute appendicitis in the newborn is rarely seen. The various authors reporting appendicitis in children all have a very limited number recorded as being under one year of age. A survey of the literature disclosed only 15 cases under four weeks of age: 6 were in hernial sacs and 9 were true intra-abdominal appendicitis. Only the six hernial sac cases recovered. The mortality decreases as the age of the patient increases: in 32 appendicitis cases 4 to 32 weeks of age, 14 recovered.—F. E. St. George.

CORRECTION

The Landoz Chemical Works, Inc., New York, referred to on page 222 of the July issue, should read "Sandoz Chemical Works, Inc."

1. Peptic Ulcer Disappearance After Feedings of Normal Human Gastric Juice

By

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THE mechanism of peptic ulcer formation within the gastric and duodenal tissue has long been argued but remains unsolved. It is the purpose of this report to demonstrate the presence of a "protective principle" within gastric mucosa whose absence leads to the formation of peptic ulcer.

John Hunter in 1778 (1) was among the first to enunciate the theory that a "vital principle" was present in the living stomach which prevented its own digestion. When Jean Cruveilier made his classic pathological descriptions of gastric ulcer, he also stated (2) (1830-42) that gastric ulcer develops because of the loss of a "local vital principle." William Beaumont's studies of the protective action of gelatin in the digesting stomach of Alexis St. Martin led him to conclude that regarding this protective action of the stomach "there were some principles in the gastric juice not susceptible to chemical examination nor to the senses." (3).

These original observations by Hunter, Cruveilier and Beaumont concerning this protective principle inherent in the stomach tissue whereby it prevents its own self-digestion or local ulceration of the gastric and duodenal lining, have remained essentially unaltered.

The modern treatment of peptic ulcer is still based on Sippy's ulcer regimen; and although more than a hundred years have passed since Cruveilier first advocated a milk diet in the treatment of peptic ulcer (4), the medical dietetic therapy has not undergone any great change since Sippy popularized it in conjunction with his powders. Babkin (5a) and others have established that the disadvantages of the Sippy regimen are two-fold. First, the frequent stimulation of the reflex phase of gastric secretion from the repeated feedings increase the gastric juice secretion.

Second, the secretion of gastric juice is further increased by the stimulatory effect of the alkali powders or tablets after their absorption.

Therefore, an attempt to introduce a new form of therapy, based on physiological principles and avoiding the disadvantages of the Sippy regimen, may be desirable.

As Babkin has stressed (5b) in recent years, considerable evidence has accumulated to show that the mucosa of the stomach and upper small intestine is protected by some principle present in normal gastric juice. Mann and Bollman (6) and Langenskiold (7) have clearly shown that this protective principle in the gastro-intestinal mucosa can be exhausted by too prolonged contact with unbuffered, dilute hydrochloric acid. Best (8) called this protective principle an "anti-ferment" and believed that it was elaborated in

the cells of the gastro-intestinal mucosa.

Successful studies which have thrown light on the search for this protective principle seem to have begun with Walawski in 1928 (9). This author found a biodialysate (fluid in which the upper intestine was kept) which inhibited gastric secretion. Simultaneously, Feng, Hou and Lim (10) first showed the presence of an inhibitory substance upon the gastric secretion from the intestinal mucosa. The name "enterogastrone" was given this substance by Kosaka and Lim (11 a, b). These authors found that following olive oil inhibitory experiments, "enterogastrone" could be extracted from the intestinal mucosa; this was also based on Ewald and Boas Findings in 1886 (12) which first showed that olive oil inhibited gastric digestion and gastric motility.

Additional studies on enterogastrone have been reported by Ivy (13) and Gray, Bradley and Ivy (14).



Fig. 8A—Roentgen silhouette of duodenal cap ulceration; before treatment.

A gastric secretory depressant in the urine named "urogastrone," has also been described by Gray et al (15) and its physiological properties further studied by Friedman and Sandweiss, (16) and others. However, despite the passage of 16 years, when the substance known as enterogastrone was first described, no practical application has been available to the profession in the treatment of peptic ulcer with enterogastrone or urogastrone.

The author felt, therefore, that additional information may be secured by a different approach in the quest for the "protective principle" inherent in stomach tissue.

*From the Gastro Intestinal Clinic, Temple University Medical School and Hospital.

PLAN OF STUDY

The author believed that it would be simplest to remove the gastric juice from normal subjects and feed this, after suitable preparation, to patients with peptic ulcer. It was felt that in this way, the protective principle in the stomach and duodenal mucosa might best be demonstrated. To this end, 6 normal volunteer male subjects were secured and large quantities of gastric juice thus obtained. These normal volunteer subjects ranged in age from 24 to 35 years of age and were free from any gastro-intestinal symptoms; they were either senior medical students or "junior internes"



Fig. 8B—Same cap after feedings of prepared normal human gastric juice; ulcer healed.

and were normal to routine physical examination. Their gastric juice acidities all fell within normal limits following stimulation by histamine. All other features of their gastric analyses were normal.

Two stimulations with histamine, 1 mg. dosage were administered subcutaneously one hour apart, to each subject. The gastric contents were collected over a three hour period of time, at fifteen minute intervals. The first gastric juice extraction, however, was discarded to avoid its pepsin content, as pointed out by Babkin (17), and to ensure only a relatively negligible amount of pepsin and mucus (18a to b).

The gastric juice was then rendered neutral by sodium hydroxide, filtered, and rendered further bacteriologically sterile by 0.3% triresol as a preservative.

A series of 10 unselected, consecutive ambulatory patients with uncomplicated gastric and duodenal ulcers were studied. Each patient had an ulcer that was roentgenologically demonstrable as a niche, a crater or an ulcer defect, in addition to the associated roentgen findings of peptic ulcer, such as spasm, increased emptying time, local pain to palpation under fluoroscopic guidance, etc. These patients were placed on a normal, well-balanced diet with no restrictions, other than the avoidance of alcoholic beverages. Smoking was permitted to those who were smokers.

One half ounce of normal gastric juice was fed to

each patient every hour diluted with two ounces of tap water, during waking hours. No other oral medication or parenteral medication of any description was given.



Fig. 12A—Roentgen silhouette of duodenal cap ulceration; before treatment.

Psychotherapy and suggestion were avoided as far as possible.

The accompanying table shows the associated gastric



Fig. 12B—Same cap after feedings of prepared normal human gastric juice; ulcer healed.

acidities, duration of ulcer symptoms, time required for symptomatic relief, time required for X-ray demonstration for healing of ulcer, etc.

It is seen that the ages of the patients ranged from 25 to 58 years with an average age of 40. There were

7 males and 3 females. The average duration of symptoms prior to this study was 9.3 years, ranging from one year to 25 years. The gastric acidities after histamine stimulation ranged from 18 units free hydrochloric acid over 46 units total acidity to 105 over 118 units gastric acidity.

Five duodenal ulcers, three pre-pyloric ulcers and two gastric ulcers were present in these 10 patients.

Symptom relief in 8 cases was 1.2 day; the average periods of time required for roentgen disappearance of the ulcers in these 8 cases was 2.1 weeks. It is interesting to note that 6 of the patients had the typical ulcer syndrome of Soupault and Moynihan; i. e. hunger-pain, food-relief in a regular rhythm coming on with mid-meal timing, etc. The other four patients had atypical clinical syndromes, consisting of constant gassy dis-



Fig. 17A—Roentgen silhouette of duodenal cap ulceration; before treatment.

Six patients had previously noted prompt relief of ulcer pain on drinking milk or taking bicarbonate of soda or alkalies.

Eight of the 10 patients responded in from 24 to 48 hours to the feeding of normal gastric juice by becoming free of ulcer symptoms. No ulcer recurrences have occurred in these 8 patients during a three year follow-up period. Two patients showed no improvement although fed with normal gastric juice for three weeks. One of these 2 patients, No. 6, had constant atypical duodenal ulcer symptoms of abdominal gassy distress and pyrosis regularly for some 19 years. The other patient who failed to respond, case number 9, had experienced pyloric ulcer symptoms for 25 years in an intermittent manner, but noted about 50% amelioration of symptoms on a strict Sippy regimen of diet and alkalies.

Of the 10 patients, six previously had proven diagnoses of peptic ulcer, while 4 were diagnosed by the author immediately prior to this study. Seven of these patients had received previous ulcer treatment and the longest periods of freedom from ulcer symptoms ranged from 4 months to 2 years, with an average of 11 months. 2 patients, cases numbers 5 and 6 previously experienced constant distress since the onset of their ulcer symptoms.

Figures 8, 12, 17 show the roentgen silhouettes in ulcer patients before and after feedings of normal gastric juice. The average period of time required for



Fig. 17B—Same cap after feedings of prepared normal human gastric juice; ulcer healed.

tress, or nausea, or pyrosis, etc. This incidence is not unusual.

COMMENT

Histamine was chosen to produce the gastric juice for the patients in these experiments because a considerable number of investigators and observers have shown that the action of histamine is dual. First, it stimulates the parietal cells to a very high gastric acidity and second, the digestive power of the gastric juice is almost completely lost (19). As Babkin (18 a, b, c) and his school have shown repeatedly, histamine stimulates the parietal cells and inhibits the discharge of pepsin and mucus from the peptic and mucosa cells respectively. They proved also that the histamine causes the rapid fall of the digestive power of the gastric juice to an extraordinary low level. Only during the first 15 minutes after histamine stimulation did pepsin and mucus appear in the gastric juice in any appreciable quantities. Bockus (20 a, b) has also pointed out the inverse ratio existing between the acid production and the mucus production of the gastric mucosa following histamine stimulation of the parietal cells in the stomach.

As Eusterman and Balfour have stressed (21), there is a great deal of evidence indicating that when the gastric mucosa is damaged by disease, the parietal cells suffer first. It appears logical therefore to seek for

the protective principle in the normal gastric mucosa as being elaborated by the parietal cells of the gastric mucous membrane. The results of the experiments herein reported tend to support this belief.

Subsequent communications will report the results of feeding an extract of the hog stomach to both dogs with induced peptic ulcer and a series of human subjects with peptic ulcer.

SUMMARY

1. The gastric juice of normal volunteer subjects was fed to a series of patients with uncomplicated peptic ulcer. The normal gastric juice was neutralized, filtered and preserved with tricresol.

2. The relief of peptic ulcer symptoms and prompt roentgen disappearance of peptic ulcer is herein recorded following the feeding of gastric juice from normal human subjects.

3. Evidence is presented which tends to indicate that a "protective principle" is elaborated within the gastric and duodenal mucous membranes and secreted into the gastric juice. This protective principle may be lacking or be impaired in patients with peptic ulcer.

4. It appears that the protective principle in normal gastric juice can be fed to uncomplicated peptic ulcer patients causing the ulcers and symptoms in these patients to disappear.

TABLE I

*Studies On Feeding Normal Gastric Juice To
Ten Peptic Ulcer Patients*

Case No.	Type of Ulcer	Age	Sex	Duration of Symptoms	Typical or Atypical Symptoms	Relief by Milk or Alkalies	Relief by Gastric Juice Feedings	Time Required for Symptomatic Relief
1.	Duodenal	28	M.	4 years	Typical	Yes	Yes	24 hours
2.	Duodenal	41	M.	9 years	Typical	Yes	Yes	48 hours
3.	Pre-pyloric	37	F.	7 years	Atypical	No	Yes	24 hours
4.	Duodenal	47	M.	13 years	Atypical	No	Yes	48 hours
5.	Gastric	33	F.	1 year	Typical	Yes	Yes	24 hours
6.	Duodenal	56	M.	19 years	Atypical	No	No
7.	Pyloric	35	M.	5 years	Atypical	No	Yes	24 hours
8.	Duodenal	40	M.	8 years	Typical	Yes	Yes	24 hours
9.	Pyloric	58	M.	25 years	Typical	Yes	No	...
10.	Gastric	25	F.	1½ years	Typical	Yes	Yes	24 hours

† Roentgenologic demonstration of crater, or niche or persistent fleck, with associated signs of ulcer.

†† Peak acidity after stimulation with 0.5 mg. histamine.

Earliest Time for X-ray Disappearance	Condition after 2 years	Previous Ulcer Treatment	Longest Previous Period without Symptoms	Ulcer Previously Diagnosed	Free HCl Total Gastric Acid
2 weeks	No recurrence	Yes	4 months	Yes	105/118
3 weeks	No recurrence	Yes	8 months	Yes	60/90
2 weeks	No recurrence	No	2 years	No	72/65
3 weeks	No recurrence	No	6 months	No	75/108
10 days	No recurrence	Yes	None	No	18/46
None	Unchanged	Yes	None	Yes	55/80
2 weeks	No recurrence	Yes	8 months	Yes	43/58
2 weeks	No recurrence	Yes	1 year	Yes	102/138
None	*	Yes	2 years	Yes	35/55
10 days	No Recurrence	No.	4 months	No	45/77

* Patient No. 9 refused surgery; symptoms moderately improved on strict Sippy regime.

REFERENCES

1. *Hunter, John* (1778), quoted in "Stomach and Duodenum" by Eusterman, G. B. and Balfour, C. D. W. B. Saunders Co., 1935; page 6.
2. *Cruveilier, Jean*, Anatomie pathologique du corps humain, Paris 1830-1842; Diseases of the Stomach, Section VII.
3. *Beaumont, William*, Experiments and Observations on the Gastric Juice and the Physiology of Digestion. Plattsburgh, F. P. Allen, 1833. pp. 228-229.
4. *Cruveilier, J.*, quoted by Brown, Ralph C. in "Ulcer of the Stomach and Duodenum," Oxford Medicine, Vol. 111, Part 1, p. 161. Vd. infra also (2) p. 124.
5. a) *Babkin, B. P.*, Secretory Mechanism of the Digestive Glands, Paul B. Hoeber, 1944, p. 352. b) idem, p. 46.
6. *Mann, F. C.*, and *Bollman, J. L.*, Experimentally produced peptic Ulcers; Development and Treatment. Jour. Amer. Med. Ass'n. 99:1576-1582 (Nov. 5) 1932.
7. *Langenskiold, F.*, Über die Widerstandsfähigkeit einiger lebender Gewebe gegen die Einwirkung eiweißspaltender Enzyme. Skandinav. Arch. f. Physiol. 120:537-550, 1913.
8. *Best, D.*, Zur Frage des Selbsterhaltung lebenden Gewebe. Beitr. path. Anat. 60, 170, 1915.
9. *Walański, J.*, Les Biodialysates intestinaux, agents inhibiteurs de la sécrétion gastrique. C. R. Soc. Biol. Paris, 99, 1169, 1928.
10. *Feng, T. P., Hou, H. C., Lim, R. K. S.*, On the Mechanism of the Inhibition of Gastric Secretion by Fat. Chin. Jour. Physiol. 3, 371, 1929.
11. a) *Kosaka, T.*, and *Lim, R. K. S.*, Demonstration of the Humoral Agent in Fat Inhibition of Gastric Secretion. Proc. Soc. Exper. Biol. N. Y., 27, 890, 1930.
b) *Kosaka, T.*, and *Lim, R. K. S.*, On the Mechanism of the Inhibition of Gastric Motility by Fat. An inhibitory agent from the intestinal mucosa. Chin. Jour. Physiol. 7, 5, 1933.
12. *Ewald and Boas*, Virchow's Arch. f. path. Anat. 104, 271, 1886; quoted in Diseases of the Digestive Systems. Portis, S. A., Lea and Febiger, 1944, p. 868.
13. *Ivy, A. C.*, The Gastro-Intestinal Hormones. Presented before the Philadelphia College of Physicians, No. 8, 1944; Philadelphia Medicine 40:487, Dec. 9, 1944.
14. *Gray, J. S., Bradley, W. B., and Ivy, A. C.*, On the Preparation and Biological Assay of Enterogastrone. Amer. Jour. Physiol. 118:463 (Mar.) 1937.
15. *Gray, J. S., Culmer, C. U., Wilczekowski, E., and Adkison, J. L.*, Preparation of pyrogen-free urogastrone. Proc. Soc. Exp. Biol. N. Y. 43, 225, 1940.
16. *Friedman, M. H. F.*, and *Sandweiss, D. J.*, Gastric Secretory Depressant in Urine. Amer. Jour. Digest. Dis. 8, 366, 1941.
17. *Babkin, B. P.*, vd. (5a), p. 270.
18. a) *Babkin, B. P.*, vd. 5 a. p. 288, 268.
b) *Alley, A.*, "The inhibitory effect of histamine on gastric secretion," Amer. Jour. Digest. Dis., and Nutr. 1, 787, 1935.
c) *Webster, D. R.*, "Changes in the Composition of the Gastric Juice under Different Stimuli." Trans. Roy. Soc. Can., 5, Sec. v, 213, 1931.
d) *Gilman, A.*, and *Cotegill, G. R.*, The determination of peptic activity: an examination and application of the Gates method of proteolytic enzyme titration. J. Biol. Chem., 88, 743, 1930.
e) *Gilman, A.*, and *Cotegill, G. R.*, "The effect of histamine upon the secretion of gastric pepsin. Amer. Jour. Physiol. 97, 124, 1931.
f) *Rasenkov, I. P.*, The mechanism of the second phase of gastric secretion. Arch. Sci. Biol. Leningrad 25, 27, 1925.
g) *Crinitz, D. I.*, The changes in the reactivity of the secretory apparatus of the stomach produced by the strength, frequency or quality of the stimulus. "On the Mechanism of Regulation of the Function of the Digestive Glands." Ed. by I. P. Rasenkov. Moscow and Leningrad, 1937, p. 1.
h) *Tumass, A. I.*, Neurohumeral relations and their disorders in the secretory activity of the stomach. On the Mechanism of Regulation of the Function of the Digest. Glands vd. 18g; p. 107.
19. *Babkin, B. P.*, Variations in the composition of the gastric juice under different conditions. Trans. Roy. Soc. Can. 24, Section V, 201, 1930.
20. a) *Bockus, H. L.*, Gastroenterology, Vol. 1, The Esophagus and Stomach; Saunders, 1943, p. 329.
b) *Helmer, O. M.*, "The relation of the secretion of mucus to the acidity of the gastric juice. Amer. Jour. Physiol. 110:28, 1934, quoted by Bockus idem (a).
21. *Eusterman, G. B.*, and *Balfour, D. C.*, The Stomach and Duodenum. W. B. Saunders Co., 1935 p. 33.

2. The Prevention Of Induced Peptic Ulcer In Dogs By Feeding A Hog Stomach Preparation

By

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IN a previous report, the essayist described the results of feeding normal gastric juice to a series of patients with peptic ulcer (1). It was shown that the peptic ulcers in these patients healed more rapidly without a Sippy regimen and that ulcer symptoms disappeared promptly. This occurred despite the lack of administration of any medication; a normal diet was adhered to in each patient who continued his regular living habits. Evidence was then presented which warranted the belief that a protective principle was elaborated from the parietal cells of the gastric mucosa which "protects" the stomach from self-digestion and from the development of peptic ulcer.

The author then attempted reduplication of these results from humans in dogs. It was felt, however, that since the protective principle from the normal gastric mucosa was secreted into the normal gastric juice, the feeding of normal gastric tissue to the ulcerated stomach might act in the same way that the feeding of gastric juice to humans did.

Accordingly, normal hog's stomachs were secured at the abattoir, cleaned and frozen immediately after slaughter; fat was removed from the stomach and first portion of the duodenum, the gastric mucosa and submucosa prepared and fed to a series of dogs as outlined below.

A series of dogs were selected for the production of peptic ulcer by the feeding of yellow cinchophen. The method of Van Wagoner and Churchill (2, 3) was adopted since they discovered that the feeding of cinchophen is the most effective means yet found of creating gastric and duodenal ulcers in dogs. These ulcers are indistinguishable from human peptic ulcers and yet their mode of production does not derange the normal anatomic relationship of the stomach and intestines as Mann-Williamson type of ulcers do.

Aside from Van Wagoner and Churchill, numerous other investigators (4, 5, 6) found that if yellow cinchophen in adequate dosage is fed regularly to dogs for a proper length of time, the typical peptic ulcer of human type can be produced in every case. This was found to be true of other animals as well (7, 8); it was further demonstrated that peptic ulceration in animals can likewise be produced by the parenteral administration of cinchophen (9, 5). Reports have also appeared on the development of peptic ulcers in humans following the administration of cinchophen (10, 11).

METHOD OF STUDY

The dogs were divided into two groups, Group 1

consisted of 10 dogs who were fed yellow cinchophen and Group 2 of 12 dogs who were fed the cinchophen in exactly the same way, but in addition were fed simultaneously each day with extract of hog $\frac{1}{2}$ pound of the hog stomach and duodenal preparation.

The group 1 dogs were well nourished and healthy varying in weight from 6 Kg. to 20 Kg. and were given the regular kennel ration plus the ration care given all laboratory animals.

Yellow cinchophen 2.5 grams, (phenylquinoline carboxylic acid, Malinckrodt) was prepared as one dose in a capsule. White cinchophen was first used but found to be ineffective for peptic ulcer production. The capsule was manually inserted in the dog's esophagus and swallowed. Each dog was given one capsule daily plus the regular kennel ration until death occurred.

The length of time before peptic ulcers developed varied considerably and began as early as 5 days, and in 1 case taking as long as four months after the cinchophen feedings were begun. As numerous investigators found (4, 5), it was noted that peptic ulcers developed in 100% of the dogs fed the cinchophen, and in every case the ulcer was identical in every way with the human ulcer (5, 6).

The following signs and symptoms were adjudged to be indicative of peptic ulcerations: 1) hematemesis; 2) passage of tarry diarrheal stools; persistent vomiting; 3) anorexia, loss of weight and weakness.

In this group 1 series, peptic ulcers identical in every respect with human peptic ulcers developed in each dog as shown in the table: five of the dogs had multiple ulcers, five had single ulcers, although in each multiple ulcers case a gastric ulcer was also present. Seven of the dogs had a chronic pyloric ulcer on the lesser curvature posterior aspect of the stomach. In two dogs a duodenal ulcer also occurred in addition to the gastric ulcer. The ulcers were all found in the "Magenstrasse" or gastric pathway along the lesser curvature. The table also shows the loss of weight in each dog which varied from 0.3 Kg. to 6. Kg. Immediately upon death of each dog, the stomach and duodenum were removed and fixed in a 10% solution of formaldehyde U.S.P. Figures 1 and 2 show the typical pyloric ulcers produced in the dogs. The animals were fed cinchophen for periods up to six weeks and then sacrificed, with the exception of one dog who was fed cinchophen for four months before being sacrificed.

Group 2 consisted of 12 well-nourished, healthy dogs who were also fed 2.5 gm. cinchophen in exactly the same manner each day for periods up to 4 months before being sacrificed. However, in addition to their regular kennel ration, they were fed extract of $\frac{1}{2}$

*From the Gastro Intestinal Clinic, Temple University Medical School and Hospital.

-pound daily of fresh hog stomach and duodenal preparation up to the time of death.

At no time did the dogs show any sign or symptoms of peptic ulcer and they appeared normal in all respects until they were sacrificed. One dog in Group 2 was explored at the time of the death of an animal in Group 1 except for two dogs who were autopsied at the



Fig. 1—Typical Pyloric Ulcer in dog stomach produced by Cinchophen feedings (Group 1). Unprotected by hog stomach preparation.

expiration of four months.

At autopsy, no peptic ulcer of the stomach or duodenum was found in any case. In eight of the dogs, however, there was present a mild to a moderate, diffuse superficial gastritis involving the lesser curvature or Magenstrasse of the stomach. The duodenum was normal. This gastritis in some instances consisted of a number of superficial, punctate hemorrhagic, pigmented patches or large patches of thick, tenacious mucus. These findings are similar although considerably milder than those reported by Stalker, Bollman and Mann (12) with the prophylactic use of a duodenal extract in cinchophen ulcers of dogs.



Fig. 2—Typical Pyloric Ulcer in dog stomach produced by Cinchophen feedings (Group 1). Unprotected by hog stomach preparation.

Figure 5 (dog 18) shows a dog stomach from Group 2 with low grade superficial gastritis. Figure 4 shows a completely normal (dog 7) dog stomach also of Group 2. In 4 of the dogs, the stomach and duodenum were normal in all respects. At death, there was no weight

loss in any dog; some dogs had gained up to 4 Kg. in weight.

COMMENT

The author has kept in mind two considerations which bear on the above results. First, that an experimentally produced ulcer may be histologically identical in structure with that in the human; but the etiologic and



Fig. 4—Dog 7 (Group 2). Normal stomach; peptic ulcer prevented by feeding hog stomach preparation in conjunction with ulcer-producing dose of Cinchophen.

therapeutic factors concerned with the human peptic ulcer may differ widely from those operating in cinchophen ulcers of the dog. Secondly, there may be unknown factors of great importance affecting the therapeutic results described above, in the hog stomach and duodenal mucosa and submucosa preparation. These unknown factors may be responsible for the successful therapeutic results reported herein, rather than the presence of a protective principle or "anti-ferment" secreted in the normal gastric juice, as the author previously suggested (1). It is also well-known that therapeutic results elicited in the lower animals do not neces-



Fig. 5—Dog 18 (Group 2). Slight superficial Gastritis; peptic ulcer prevented by feeding hog stomach preparation in conjunction with ulcer-producing dose of Cinchophen.

sarily hold true in the human.

However, it is felt that the results obtained in this study warrant further investigation into the therapeutic effect on human peptic ulcer by a hog stomach and duo-

denal preparation used in the treatment of peptic ulcer in the dog. A preparation of this type for human peptic ulcer has already been employed therapeutically and with success by Rivers (13) in 1935 and Schmassmann (14) in 1944.

SUMMARY

1. A series of dogs in one group were fed "yellow" cinchophen; each dog developed peptic ulceration, which was indistinguishable from peptic ulcer in humans.

2. A series of control dogs in another group was also fed yellow cinchophen in exactly the same way, but in addition, the dogs were fed a mucosal and submucosal preparation from the hog's stomach and duodenum.

3. The dogs in the group which were fed the hog stomach and duodenal preparation with cinchophen did not develop peptic ulcers as did the dogs in the group who were fed the cinchophen alone.

4. It is suggested from these preliminary experiments that some support is present for the previously reported belief of the author that a "protective principle" is elaborated by the human gastric mucosa and that this "protects" the stomach from self-digestion, and ulcer formation.

5. A "protective principle" may also be contained in the mucosa of the hog's stomach and duodenum which was effective in preventing peptic ulcers in dogs whose controls had induced peptic ulcers indistinguishable from human peptic ulcers.

TABLE — GROUP 1*

Dog No.	No. of Doses & experiment days	Initial Wt., Kg.	Wt. at Death, Kg.	Wt. Loss, Kg.	Ulcers Multiple or single	Location of Ulcers	First appearance of ulcer symptoms days	Total Dose Gm.
1.	20	16.6	12.2	4.4	Multiple	Pyloric Stomach Stomach	6	50
2.	30	12.1	8.7	3.4	Multiple	Duodenum Pyloric	14	75
3.	24	11.0	6.2	4.8	Single	Stomach	18	60
4.	8	8.0	7.7	0.3	Single	"	5	20
5.	4	13.3	10.5	2.8	Multiple	Duodenum	29	100
6.	15	9.1	7.2	1.9	Single	Pyloric	7	37.5
7.	26	6.0	5.1	0.9	Multiple	Stomach	13	67
8.	46	17.7	11.0	6.7	Multiple	"	24	115
9.	122	20.1	18.3	1.7	Single	Pyloric	120	30.5
10.	11	7.8	7.0	.8	Single	"	8	27.5
Average	34	12.2	9.4	2.8			24	86

* Daily Dose 2.5 Gm. Cinchophen

REFERENCES

- Morrison, L. M.: Peptic Ulcer Disappearance Following Feedings of Normal Gastric Juice. Amer. Jour. Digest. Dis. 12:323, Oct. 1945.
- Churchill, T. P., and Van Wagoner, F. H.: Cinchophen Poisoning, Proc. Soc. Exper. Biol. and Med. 28:581-582 (Mar.) 1931.
- Van Wagoner, F. H., and Churchill, T. P.: Production of Gastric and Duodenal Ulcers in Experimental Cinchophen Poisoning in Dogs; Arch. Path. 14: 860-969 (Dec.) 1932.
- Bollman, J. L., and Mann, F. C.: Experimental Production of Gastric Ulcers, Pro. Staff Meet Mayo Clinic. 10:580-582 (Sept. 11) 1935.
- Stalker, L. K., Bollman, J. L., and Mann, F. C.: Experimental Peptic Ulcer Produced by Cinchophen; Methods of Production. Arch. Surg. 35: 290 (Aug.) 1937.
- Simonds, J. P.: Mode of Origin of Experimental Gastric Ulcer Produced by Cinchophen, Arch. Path. 26:44 (July) 1938.
- Schwartz, S. O., and Simonds, J. P.: Peptic Ulcers Produced by Feeding Cinchophen to Mammals Other than the Dog. Proc. Soc. Exper. Biol. and Med. 32: 1138-1134, 1935.
- Cheney, G.: Cinchophen Gastric Ulcers in Chicks. Arch. Int. Med. 70: 532-557, (Oct.) 1942.
- Hanke, Hans: Experimental Production of Acute Ulcerative Gastritis by Parenteral Administration of Atophenyl. Internat. Clinics. 1: 233-236, (Mar.) 1935.
- Reah, T. G.: Cinchophen Poisoning, Lancet 2:504, 1932.
- Bloch, L., and Rosenberg, D. H.: Gastric Ulcers Associated with Cinchophen Poisoning, Amer. Jour. Digest. Dis. and Nutrition 1:29, 1934.
- Stalker, L. K., Bollman, J. L., and Mann, F. C.: Prophylactic Treatment of Peptic Ulcers Produced Experimentally by Cinchophen, Amer. Jour. Digest. and Nut. 3:822, (Jan.) 1937.
- Rivers, A. B.: The Use of Duodenal Extract as an Adjuvant in the Treatment of Benign Peptic Lesions. Amer. Jour. of Digest. Dis. and Nut. 2:189, (May) 1935.
- Schmassman, Hector: Ueber die interne Behandlung des Ulcus Ventriculi und Ulcers duodeni mit den Magendiindarmpräparaten Rohuden. Schweiz Med. Wochenschr. 74:576, (May 27) 1944.

The Diaphragm In Abdominal Decompression

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THE human diaphragm is the muscle commonly known and recognized as the organ controlling the respiration. Does it possess other functions, and how are they to be understood? Moreover, how can they be utilized therapeutically?

The diaphragm is a striated muscle separating the thoracic and abdominal cavities. Relaxed it has a dome like shape, its concavity facing the abdomen. In contracting it shortens its muscle fibers, and in so doing it assumes more or less a disk shape, simultaneously descending into the abdominal cavity.

Being a striated muscle, the diaphragm is subject to cortical impulses and can be moved at will. However, unlike all the other striated muscles, it retains its full, coordinated function at a time when our voluntary control of striated muscles has partially or entirely ceased, during general anesthesia and in coma. The cessation of diaphragmatic function causes death.

Many theories have been proffered to account for this ambivalent position of the diaphragm. One of the most stimulating theories is that of S. Keith, quoted by Hitzenberger (1). Keith proved that the diaphragm is phylogenetically a circulatory, not a respiratory muscle. In amphibians the lungs are in the abdominal, not in the thoracic, cavity. In those animals the diaphragm, in contracting, lowers the intrathoracic pressure and increases the afflux of blood into the pericardial sac.

Hitzenberger (1) showed that there are several areas of the diaphragm which are not necessarily synergists. The ventral branch of the diaphragm may ascend while the dorsal branch descends. This phenomenon apparently accounts for the fact that on X-ray films the diaphragm, particularly in inspiratory position, appears on two different levels on either side (Fig. 1). Hitzenberger claimed that the action of the diaphragm influences the peristalsis of the stomach and of the intestines. Dillon (2) stated that a healthy and young diaphragm by its excursions changes the shape of the stomach and of the splenic flexure and has an important effect on peristalsis and particularly on the expulsion of gas from the splenic flexure. This statement, particularly as far as shape and peristalsis of the stomach is concerned, is borne out by our everyday fluoroscopic observation. In an attempt to stimulate pylorus play the examiner does well in asking the patient to exhale and to remain in this position for several seconds. However, the opposite can be observed occasionally too. Dillon further stated that a flabby diaphragm is incapable of expelling gas from the splenic flexure. On the contrary, as a flabby diaphragm is unable to close its muscular interstices, it will in inspiratory position transmit the negative intrathoracic pressure to the upper abdomen and this way encourage aspiration and accumulation of air in the splenic flexure.

Byloff (1) called attention to the fact that in supine position the diaphragm is 3-6 cm higher than in erect or prone position. Of this phenomenon, too, our X-ray films give ample evidence (Fig. 2 and 3). Hitzenberger found that in lying position on either side the underlying diaphragm reaches much higher into the thorax than the overlying. This may be the reason why cardiacs so often have difficulty in sleeping on their left side. Byloff also observed descensus of the diaphragm progressing with the aging of the individual.

There seems to be by now consensus of opinion that the diaphragm, in inspiratory position, narrows and at times closes the hiatus esophageus. This makes it clear why we inhale before coughing and sneezing, and why we exhale before vomiting. Knowledge of this fact also should induce us, in a search for a hiatus hernia, to examine the patient after exhaling.

There are not many true intrinsic diseases of the diaphragm known to us. Well known is trichinosis of the diaphragm. Long described has been the elevation of the left diaphragm. Less often observed and still less described is the "Relaxatio Diaphragmatis", a condition in which the left diaphragm is so far over-distended that it appears as high up as the second thoracic vertebra. On autopsy the diaphragm is paper thin and bare of any muscular structure. It consists practically of pleura and peritoneum. This is a serious condition and of fatal prognosis. Both the elevation and the relaxation of the diaphragm are considered the results of excessive and continuous distention of the stomach with air (1).

An attempt to examine the role of the diaphragm in the control of intra-abdominal pressure should be preceded by a few general and theoretical observations.

Pressure studies in the abdominal cavity have been very rarely performed and reported. The reason for this scarcity lies mainly in the difficulty and complexity of the subject. In the strict physical sense the questions may well be asked: Is there such a thing as intra-abdominal pressure? Can the abdominal cavity be considered as one physical unit? First of all, there is no abdominal cavity in the physical sense, except in the case of ascites or peritonitis, where there is a cavity filled with liquid, or air, or both. With this exception the abdominal wall surrounds a multitude of organs tightly adjacent to each other and tightly adjacent to the wall. The interspaces between two organs, or between an organ and the abdominal wall, are merely theoretical minute slits. The serosa with its moisture sees to it that no friction takes place on the one hand, and that no spaces are created on the other hand. Furthermore there are so many viscosities in the abdomen, which by contraction and relaxation create their own particular pressures and transmit these

pressures to their immediate surroundings that it seems a rather daring undertaking to introduce the term intra-abdominal pressure.

And yet, there cannot be any question as to the existence of an overall intra-abdominal pressure, and that the only organ capable of increasing or diminishing this pressure is the diaphragm. That this is so can be seen from every day experience. The individual trying to expel a hard stool, the woman in labor, and the prostatic in urinating, they all learn from experience what increase of intra-abdominal pressure can



Fig. 1—Showing the different layers of the diaphragm, after inhaling in prone position. Lines retraced for clearness.

accomplish. The well known mechanism consists in (a) inhalation, (b) closing of the glottis, (c) contraction of the muscles of the abdominal wall.

Why do we inhale before an attempt at expulsion? Any experiment on ourselves will show that, unless we inhale, there is not sufficient pressure for expelling. There also will appear an unpleasant sensation in our lower chest apparently due to the squeezing of abdominal organs into the diaphragmatic dome.

This conception of the role of the diaphragm in the control of intra-abdominal pressure was borne out by Winkler (33). In a series of experiments Winkler employed the following method. A troicart was introduced into the abdomen. The troicart then was connected with a manometer by a rubber tube. Winkler recorded a rise of the intra-abdominal pressure when the diaphragm descended, and he recorded a fall of the pressure when the diaphragm ascended. This fall of the abdominal pressure on the ascensus of the diaphragm was absent when the muscles of the abdominal wall were too active and tense. Winkler also recorded a difference in the abdominal pressure in both phases depending on the state of filling of the stomach and of the intestines.

Let us now examine the several ways and means the organism has at its disposal for elevating the diaphragm.

That exhaling will lower the intra-abdominal pressure has just been proven. The mechanism of exhaling, its beneficial effect, and its utilization will be examined further down. As it is the simplest and

most logical way of abdominal decompression, it should be expected to be more widely utilized than any other one. But, unfortunately, this is not the case.

The most devious, but by far the more popular, way of abdominal decompression is that of eructation. The full understanding of its mechanism, of its effect on the digestive tract, and of the many misconceptions that exist on this subject require another excursion into the field of anatomy and physiology.

The first question is that of the origin of "gas" in our upper gastrointestinal tract. This question has challenged medical observation and thinking since the time of Hippocrates (3). The presence of excessive amounts of air in the stomach and its ejection through the mouth was considered a disease called *morbus ructuosis* or *pneumatosis ventriculi*. Van Helmont (5) repeated this nomenclature in 1648. Combalusier (6), in 1747, was to our knowledge the first one to contradict the pathogenic significance of gas in the stomach and intestines. Magendie (4) was the first author to claim that gas in the stomach was atmospheric air which was swallowed and then returned through eructation. Since Magendie's publication papers have been published on this subject in ever increasing numbers. A study of the entire world literature with a comprehensive bibliography till 1918 can be found with Kantor's article (4). An extensive survey and bibliography from the X-ray standpoint can be found in an article by Barsony and Koppenstein (27). According to Rieder (7) it was Bouveret who, in 1891, created the word aerophagy, and it was Oser who first described the aspiration of air into the stomach. Ewald, in 1910, reported on a patient whose ructus were inflammable. Spivak (9) quoted A. M. Farmington, acting chief of the Bureau of Animal Industry, U. S. Department of Agriculture, as saying that air swallowing by horses is well known under the names "cribbing" and "wind sucking". Ten years before Spivak, Wyllie (10) had reported the same observation on calves, horses, and oxen. Wyllie also noticed air sucking by babies, particularly when the nursing bottle was empty. Perfectly beautiful X-ray studies on air sucking by newborn babies were done by Lelong and Aime (29). Wyllie was the first author to state that suction is a means by which air is transported into the stomach. He called this mechanism "inructation". Thiele (11) showed that the stomach and intestines in stillborn babies is free from gas, and that in newborn babies gas has entered the stomach and even passed into the intestine after a few minutes of life. Wolff (12) reported on the death of a 3 months old baby that had continuously swallowed air, except when profoundly asleep. The baby's abdomen was tremendously distended, and its head and extremities looked only like tiny appendices to the huge abdomen. Autopsy revealed nothing but a dilated stomach and intestine. McIver et al. (13) stated that swallowed air is the principal source of gaseous distention of the stomach and intestine after abdominal operations. Wangenstein and Rea (14), in 1939, in a classical experimental study with exclusion of swallowed air by cervical esophagostomy, showed that practically no

distention proximal to artificial mechanical intestinal obstruction takes place in dogs after esophagostomy.

As to the chemical nature of "gas" in the stomach and upper intestines, there seems to be general agreement that this gas is atmospheric air, with a slight increase of carbon dioxide which according to Dunn and Thompson (15) can be accounted for by secretion or diffusion from the gastric mucosa. In order to determine the possibility of fermentation as a source of stomach gas, Dunn and Thompson performed the following experiment. Gastric contents, obtained after the usual Ewald test breakfast from 100 unselected cases were incubated at 37°C for 24 hours in saccharimeters. In only 31 instances was there any evidence of gas formation as shown by a large or a few minute bubbles. In 17 cases only was there a bubble of sufficient size to estimate. In all cases except three, in which there was any evidence of gas production there was no free hydrochloric acid present. In the 3 cases that showed gas in the presence of free hydrochloric acid the total acidity was below 20. Dunn and Thompson concluded from this experiment that fermentation can have little to do with the carbon dioxide content of the stomach gas. In summarizing this experiment by Dunn and Thompson we may state that there was:

- (a) practically no fermentation in the presence of free hydrochloric acid.
- (b) some fermentation after 24 hours in the absence of free hydrochloric acid, of which in only 17 of 31 cases (54.8%) was the gas bubble large enough even to estimate.

This opinion of Dunn and Thompson was confirmed by Hurst (26) who in a comprehensive survey stated the following: "Due to the inhibiting action of free acid on bacterial activity and the continuous passage of food into the duodenum, fermentation cannot occur. We have found that even in complete achlorhydria very little gas is produced by fermentation unless pyloric obstruction is also present". We may therefore conclude: Only in an anacid stomach that retains its contents for 24 hours any appreciable degree of fermentation takes place. This means for clinical purposes that only in the late stage of carcinoma, obstructing the pylorus, do we have to expect any amount of gas formation within the stomach.

Fine and Starr (16) go still further. They state that of the total amount of gas accumulating in the intestine, 90% is absorbed and exhaled through the lungs while the remainder is expelled by rectum. Hoppe-Seyler (17), in 1892, had already found that "in certain cases of gastric dilatation" (no diagnosis was given) carbon dioxide and hydrogen were found in the stomach. His opinion was that the hydrogen formation was due to butyric acid fermentation. Hydrogen may have been the gas causing "inflammable eructation" in Ewald's patient. (see above). Gerardin (18), Chevillot (19), and Magendie and Chevreul (20), proved that carbon dioxide can occur in a normal stomach. Schierbeck (21) believed that carbon dioxide is always present in a normal stomach and explained this phenomenon solely by the tendency of the atmos-

pheric air in the stomach to establish an equilibrium with the much higher carbon dioxide level of the tissues and of the blood. Schierbeck claimed that it is diffusion through the stomach wall, not fermentation, that accounts for the presence of carbon dioxide in the stomach. That gas can permeate the stomach wall, be it through excretion or diffusion, was also proven by Ramond, Zizine, and Vanier, quoted by Pron (22). These authors ligated the cardia and the pylorus in dogs and injected ether into the blood stream. They recovered ether gas from the stomachs. The same

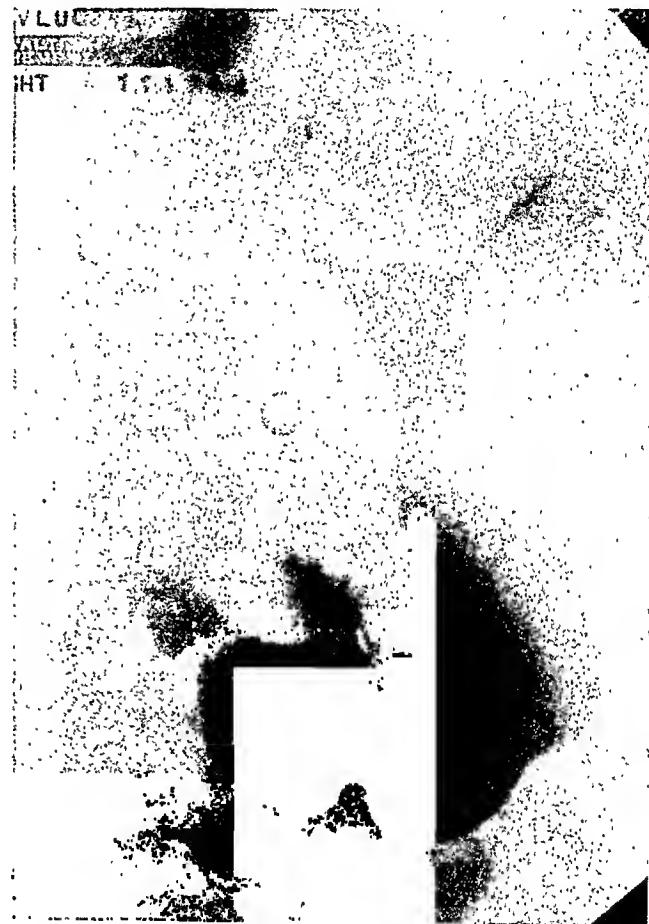


Fig. 2.—In erect position after inhaling the diaphragm reaches the height of the upper border of the 12th thoracic vertebra.

phenomenon was demonstrated in the opposite direction by Ylppoe (37). This author introduced at different times atmospheric air, carbon dioxide, or oxygen into the stomach. After a while the values for carbon dioxide and oxygen in the stomach became the same as those in the blood.

With the backing of so many authors we may now summarize: Except in terminal cases of pylorus carcinoma, "gas" in the stomach is atmospheric air carried down through the pharynx and the esophagus.

Why have so many authors felt the necessity of stating and proving this fact? It is because there has been, and still is, a wide spread belief within our medical profession and in the public that gas is developed in the stomach, and that it must be expelled by belching. "Gas" is the daily complaint in the gastroenterologist's

office, and unfortunately this term is still all too popular in our hospital records. This deplorable fact induced Gallart-Mones and Pinos (30) as late as 1931 to write an article entitled "Does Aerophagy Exist?" Leven (31) wrote an article on the existence of aerophagy still seven years later.

The question of how the air is transported into the stomach has challenged another host of authors throughout the centuries. As this question plays only a secondary role in our considerations, we may be permitted to summarize.

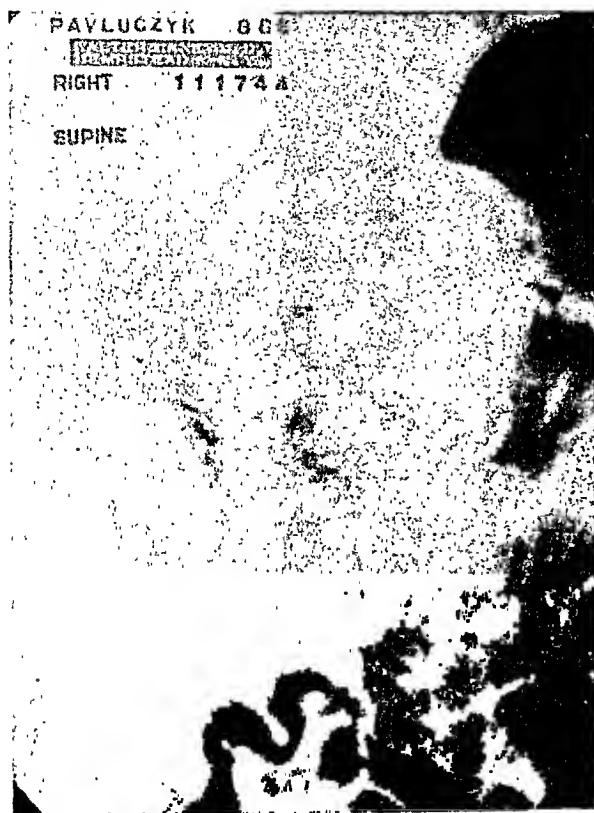


Fig. 3—In the same patient in supine position after inhaling the diaphragm reaches the height of the lower border of the 9th thoracic vertebra. Notice the barium filling the fornix and the cardia bud while the air is escaping through the caudal half of the stomach into the duodenum.

There are three possibilities of air transport into the stomach;

- Swallowing air while swallowing food or liquids. This is commonly done by all mankind and is the feeder of the "magenblase". This habit however is occasionally overdone.
- Swallowing air alone. No proof has been offered as to the existence of swallowing air alone. If it is done, the air is immediately returned by the upper esophagus.
- Aspirating air while the glottis is closed. This constitutes the actual act of belching.

Belching may be called an ingenious misuse of facilities nature has endowed us with. Belching is ubiquitous. We all do it occasionally, and it would not be worth writing about it if it were not for the fact that there are numerous people whose belching reaches

a state of a compulsive bad habit, of a tic (22), of an obsession (23). Here is in short the mechanism.

Inructation.—The glottis is closed, the chest is dilated by way of the intercostal muscles, while the diaphragm remains in "neutral". The thus created negative thoracic pressure opens the normally collapsed esophagus and cardia and lets the air pass into the stomach. This can be observed on fluoroscopy. (Figure 4). Through the dilated esophagus and cardia air streams into the stomach while the upper level of the barium meal is forced downward, at times assuming funnel shape (vortex formation?).

Eruetation.—Immediate return of the air through the esophagus simultaneous with the ascensus of the barium level and the elevation of the left diaphragm. Please note carefully the elevation of the left dia-phragm as we will return to it further down.

That there is no eructation without inructation was stated by Leven (32). That this is true can be demonstrated. It is well known that, in supine position, after eating or after a barium meal, the fornix ventriculi and the cardia bud are filled with food or liquid because they are low. The air rises toward the caudal end of the stomach because it is high (Figure 3).

Another observation seems to yield information relevant to this matter. In performing gastroscopy the patient is put in prone oblique position. In this position the fornix and the cardia are high, and the pylorus is low. Air in the stomach is therefore easily expelled through eructation. In performing esophagoscopy the patient is put in supine position. In this position the fornix and the cardia are low, and the pylorus is high. Whereas the entrance of gastric contents into the esophagus is often observed according to Smith and Coon, no air is expelled from the stomach on esophagoscopy.

We believe to have shown that air can have no access from the stomach to the esophagus in supine position and yet, the individual wishing to belch in supine position can do so lustily, and we see this being done by many of our bed-patients.

The air is sucked into the stomach and then returned, if possible. What is not returned, because it has already ascended to the pylorus, later accounts for distention as so often seen after laparotomy. Barsony and Koppenstein (27) observed fluoroscopically eructation by patients who kept only their esophagus filled with air and did not even let the air pass into the stomach.

Why do people belch? Lyon (23) stated: "It is required for becoming aerophage to have epigastric tension of which belching affords transitory relief". Becart (24) suggested the looking out for organic lesions. The same was suggested by Katsch, quoted by Dyes (25). Katsch claimed that 60% of patients with aerophagy suffered from organic lesions. Vogelius explained the whole syndrome by the desire of the patient to get rid of some kind of discomfort through belching of air "swallowed" for the purpose of belching.

The answer to the question of why people belch now seems clear. People have some kind of discomfort and know from experience that belching gives them transitory relief. It is entirely conceivable, although not

proven, that already during the eructation the negative thoracic pressure is transmitted to the upper abdomen. It is certain however that during eructation which is accompanied by elevation of the left diaphragm, the intra-abdominal pressure decreases.

And for this short moment of relief and enjoyment, so many people go through the ugly procedure and say every time "pardon me", as if this stereotyped formula made them sociable which they are not, and they know it.

May we summarize: Belching is a means of relieving oneself from a sensation of abdominal discomfort. This relief is afforded by elevation of the left diaphragm which entails abdominal decompression.

After we have devoted so much space to this devious and strange way of abdominal decompression, let us return now to the above mentioned simpler way: Exhalation. In doing so we will notice to our embarrassment that, whereas the literature is filled to abundance with articles on eructation, expiration has found only very few advocates.

It was Hofbauer (34) who, to our knowledge for the first time, called attention to the importance of the diaphragm for the abdominal organs. He made the following statement, "The action of the diaphragm in conjunction with the musculature of the abdominal wall produces the effect of a massage of the abdominal contents, and also of a support for the abdominal blood circulation as well as for peristalsis". And specifying on the importance of expiration he stated, "The usually employed form of deep inspiration is distinctly injurious." In a book devoted to this subject (35) Hofbauer made the following remarks, "Prolonged exhalation helps the transport of secretion out of the great abdominal glands (he was referring to the liver, the pancreas, and the kidneys, W.C.) as well as the blood reflux through the vena cava inferior and the lymph transport (through the thoracic duct, W.C.). Prolonged exhalation also affects favorably the motor activity of the gastrointestinal tract, particularly through increase in the tonus of the muscles of the abdominal wall." Hofbauer puts great stress on the importance of prolonged exhalation without the use of too much contraction on the part of the muscles of the abdominal wall. Becart (24) advocated breathing exercises for the treatment of aerophagy. Unzer (36) in 1759 had already suggested physical exercises in the open air for the cure of pneumatosis ventriculi.

For several years it has been our desire to find a new, simpler way to help patients with abdominal discomfort and at the same time to free them from their bad habits of belching which we had learned to consider a make-shift help with definitely injurious consequences. We had convinced ourselves that air in the stomach enters the intestinal tract as soon as the patient lies down, and that this air is largely responsible for abdominal distention. Simulated by Hofbauer's suggestions we discovered one day that nature herself had already invented and put into practice this author's ideas. The discovery was made by observing people in acute abdominal distress. Long and careful observation revealed that eructation is

practised by people only up to a certain degree of discomfort or pain. If these sensations become overpowering and hardly bearable, the patient stops belching and starts groaning. We will hardly hear a patient groan from pain due to chronic gastric ulcer, cirrhosis of the liver with ascites, kidney tumor, ovarian cyst, or after an uncomplicated laparotomy. Those people, if they do have abdominal discomfort, will often try to relieve themselves by belching. However, a groaning patient will immediately direct our thinking toward

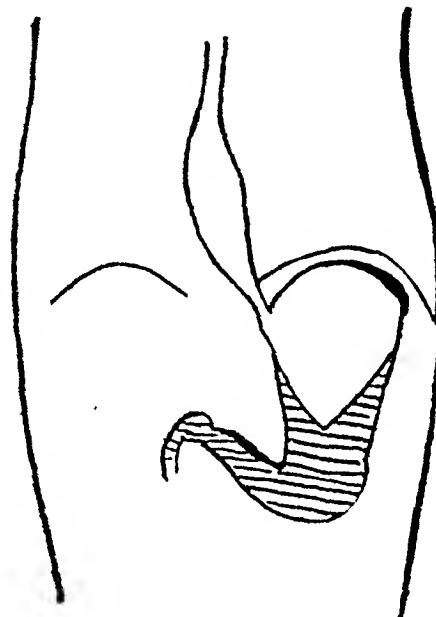


Fig. 4a—Showing spindle like dilatation of the esophagus while air streams into the stomach. Barium level is lowered and assumes funnel shape.

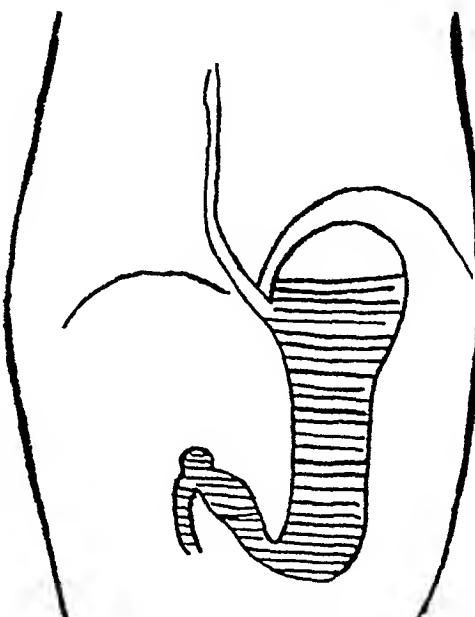


Fig. 4b—Air has just escaped through esophagus while left diaphragm is still elevated.

perforated ulcer, gallbladder attack, kidney stone, or acute peritonitis. Yes, even the woman in labor, trying to relieve herself from her pains, will groan.

We may therefore draw the conclusion that groaning affords better and more effective relief from

abdominal pain than belching. Close observation of a groaning patient will reveal that he unknowingly follows to the letter the directions given by Hofbauer. Groaning is accomplished by comparatively short and not too deep inhalation followed by slow and prolonged exhalation. In exhaling, the patient does not apply any pressure from the muscles of the abdominal wall. Yet, in his desire longer to enjoy the relief exhalation can give him, the patient is still more inventive. He narrows his glottis by adducting his vocal cords, and this "trick" affords him the possibility to let the air out slowly and gradually. The adduction of the vocal cords causes the tone that accompanies the act of groaning.

In following Hofbauer's suggestions as well as the lead nature herself has given us, we found the following method to be useful. The patient is directed to take short and not too deep inhalations followed by prolonged exhalations. If desired, the patient may remain for a few seconds in expiratory position before inhaling again. In order to facilitate prolonged exhalation the same trick can be applied that a groaning patient uses. It was obvious from the start, however, that it was impossible to get a not too sick patient to perform actual groaning. A method of narrowing the glottis without producing a tone was to be taught. The patient was told that the method to be applied is related to groaning as whispering is related to regular speech. After the patient has practised whispering, he is directed to do the same without saying words. He will then inhale and exhale with the slurring, toneless noise that characterizes whispering.

After this has been learned, the patient is told to inhale the ordinary way and to exhale the "whispering" way. If he has done this for awhile, he is directed to take short and hearty, but not forced deep, breaths and to exhale in the now familiar way with the effect of prolonged exhalation.

After a short time of practice the patient will learn

to use his new exhaling technic in such a moderate way as to make the stridor nearly inaudible. If this is learned, the patient will feel safe breathing the newly learned way, without running the risk of his new method being noticed by other people.

It has proved to be advisable to direct the patient to practice the new breathing technic any time of the day he feels the desire to relieve himself of his abdominal discomfort or pain.

In discussions with colleagues the objection was occasionally heard that artificial azotemia will be created by prolonged expiration. That this is not so can be demonstrated by breathing the described way indefinitely. No sensation of smothering will appear.

After having employed this breathing technic over several years, it may be stated that there has not been any condition the gastroenterologist runs across that had not been benefited by the method. For this reason it seems unnecessary to add case reports which are at hand. However, it appears worthwhile mentioning that the method has proved effective in completely freeing people from their bad habit of belching. It also is helpful in hospitals in teaching patients to stop groaning and this way make life more bearable for their room mates. It has proven effective in an effort to prevent post-operative gastric distention as well as in the alleviation of singultus. However the post-operative cases observed are too few to be of statistical value. Observations by abdominal surgeons on this subject will be very helpful and will be greatly appreciated.

A few remarks on the anatomy and physiology of the diaphragm were made.

An attempt was made to examine the role of the diaphragm in the control of the intra-abdominal pressure.

The syndrome of eructation was studied with all of its implications.

A method of controlled respiration was suggested for the alleviation of abdominal discomfort or pain.

REFERENCES

1. Hitzenberger, K.: *Das Zwerchfell im gesunden und kranken Menschen*. Vienna, 1927, (J. Springer).
2. Dillon, J.: *Erg. d. med. Strahlenforsch.*, III, 289.
3. Hippocrates: *Des vents*, by Littré (quoted by Kantor).
4. Kantor, J. L.: *Am. J. Med. Sc.*, 1918, 155: 829.
5. Van Helmont, J. B.: *De statibus*, Amsterdam, 1648 (quoted by Kantor).
6. Combalusier: *Pneumopathologia*. Paris, 1747, (quoted by Kantor).
7. Rieder, H.: *Muench. Med. Wch.* 1917: 1353.
8. Ewald, C. A.: *Dtsch. Med. Wch.* 1910: 641.
9. Spivak, C. D.: *Med. Record*, 1905: 649.
10. Wyllie, J.: *Edinb. Hosp. Rep.*, 1895, 3: 21.
11. Theile, P.: *Ztschr. f. Kind.* 1917, 15: 152.
12. Wolff, S.: *Jahrb. f. Kind.* 1925, 108:67.
13. McIver, M. A., Benedict, E. B., Cline, I. W.: *Arch. Surg.* 1926, 13:588.
14. Wangensteen O. H., Rhea, C. E.: *Surg.*, 1939, 5:327.
15. Dunn, A. D., Thompson, W.: *Arch. Int. Med.* 1923, 31.
16. Fine, J., Starr, A.: *Rev. Gastroent.*, 1939, 419.
17. Hoppe-Seyler, G.: *Dtsch. Arch. Klin. Med.* 1892:50.
18. Gerardin, P.: *Nouv. Bull. soc. philomat.* 1811.
19. Chevillot: *Arch. gen. med.* 1834:285.
20. Magendie & Chevreul: in Berzelius: *Lehrb. d. Chemie*, 9:338.
21. Schierbeck, N. P.: *Scand. Arch. Phys.* 1891: 3.
22. Pron, L.: *Rev. gen. clin. et ther.* 5/2, 1936.
23. Lyon, G.: *Presse Med.*, 1917, 25:676.
24. Becart, M. A.: *Bull. mem. soc. med. Paris*, 1932:524.
25. Dyes, O.: *Fortschr. Roentg.*, 1930, 42:364.
26. Hurst, A.: *Harveian Lecture*, *Brit. Med. J.*, 1938, 1:661.
27. Barsony, T., Koppenstein, E.: *Roentgenprax.* 1934, 6:425.
28. Vogelius, F.: *Hospitalstidende*, 1909:44.
29. Lelong, M., Aime, P.: *Bull. soc. ped. Paris*, 1935, 33:231.
30. Gallart-Mones, F., Pinos, A.: *Arch. med. app. digest.*, 1931, 21:382.
31. Leven, G.: *Presse med.*, 1938, 46:869.
32. Leven, G.: *Presse med.*, 1919, 27:184.
33. Winkler, F.: *Pflueg. Arch. ges. Phys.*, 1903, 98:163.
34. Hoibauer, L.: *Med. Journ. Rec.*, 4/15, 1925.
35. Hofbauer, L.: *Atmungspathologie und therapie*. Berlin, 1921, (J. Springer):264.
36. Unzer, J. A.: *Der Arzt*. 1759. (quoted by Ewald).
37. Ylpoe, A.: *Muench. Med. Wch.*, 1916, 632:1650.
38. Smith, H. B., Coon, E. H.: Personal communication.

Action Of Histaminase Preparations In The Heidenhain Dog[†]

By

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A METHOD for the partial purification of histaminase has been recently described (1). When this was simultaneously with a lethal dose of histamine one third of the animals survived (2). The concentrated histaminase preparation was injected into guinea pigs

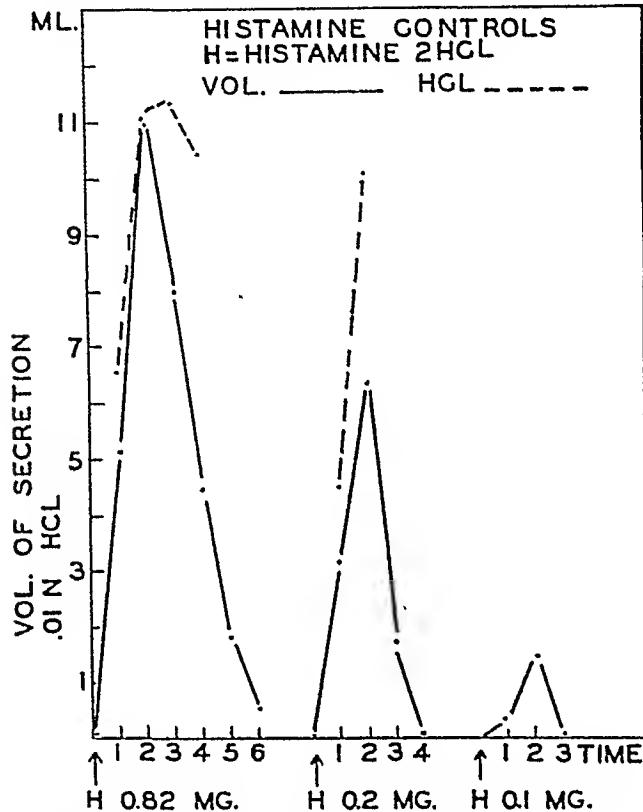


Fig. 1.—The secretory response of the gastric pouch to different doses of histamine: 0.82, 0.4, and 0.2 mg histamine dihydrochloride subcutaneously.

taminase, however, was proved to be highly toxic and could not be used in amounts sufficient to afford complete protection to guinea pigs injected with fatal doses of histamine.

It was hoped that the dog would prove to be less susceptible to the toxic ingredients of the preparation. Therefore it was decided to investigate the action of histaminase on gastric secretion induced by histamine in the Heidenhain dog.

This problem has been previously investigated by other workers (3) and (4) who concluded that histaminase does not inhibit histamine-induced secretion. However, the amounts of histaminase used in these earlier experiments were entirely inadequate (2).

Methods.—Heidenhain dogs were prepared according to the classical method and allowed to recover normal

digestive function. Prior to the experiments with histaminase the dogs were tested for response to histamine alone and found to secrete quantitatively (Fig. I).

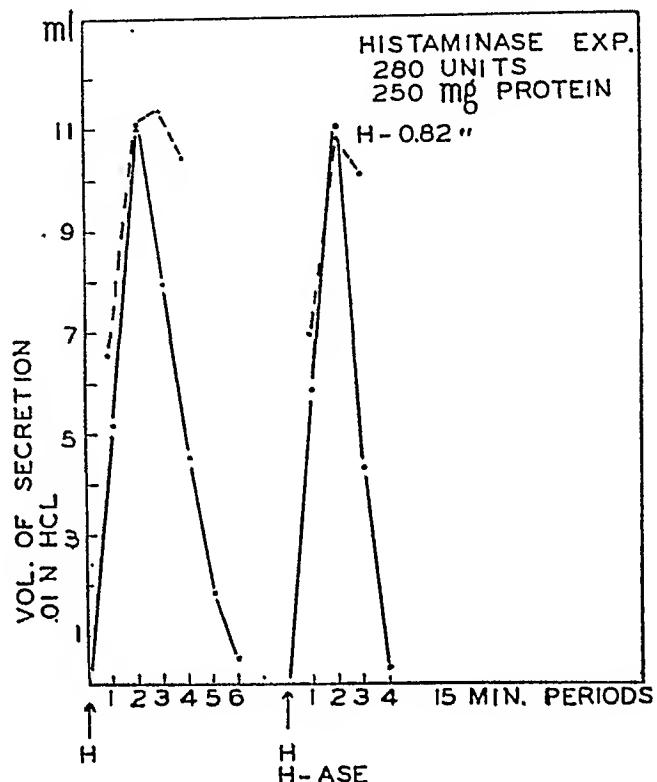


Fig. 2.—Secretory response following the intravenous injection of 280 units of histaminase and subcutaneous injection of 0.82 mg histamine dihydrochloride.

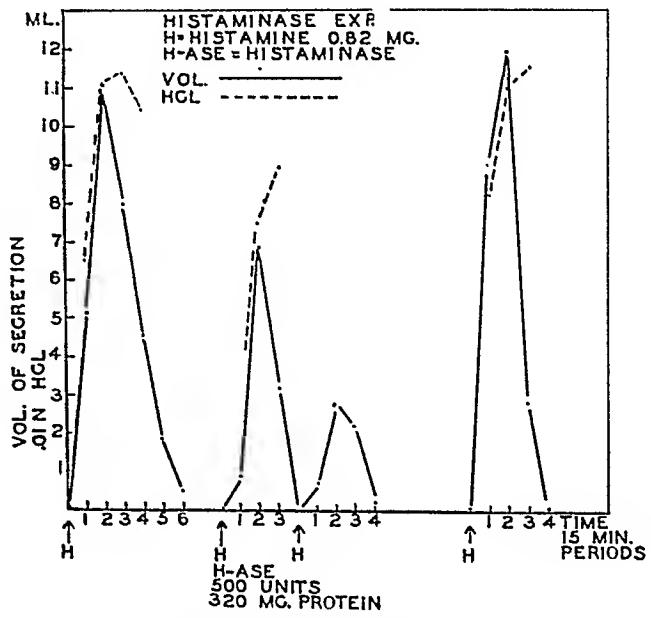


Fig. 3.—Secretory response following Intravenous Injection of 500 units of histaminase and repeated subcutaneous injections of 0.82 mg histamine dihydrochloride.

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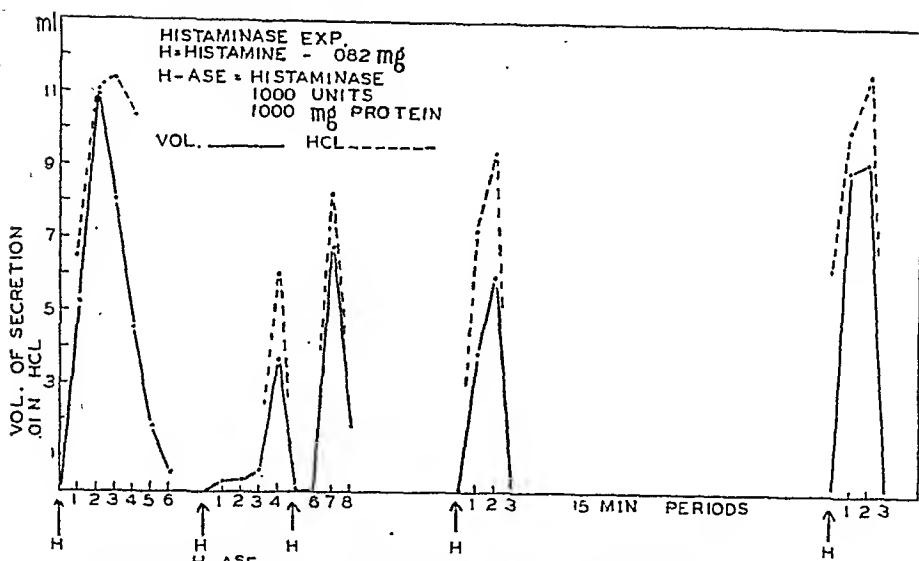


Fig. 4—Secretory response following intravenous injection of 1000 units of histaminase and repeated subcutaneous injections of 0.82 mg histamine dihydrochloride.

Histaminase experiments were carried out as follows. A known amount of histaminase, prepared according to the method described (1), having a potency of at least one unit per milligram of protein, was injected intravenously, and followed immediately by the usual subcutaneous injection of 0.82 mg of histamine dihydrochloride.

Collections of gastric pouch juice were made at 15 minute periods during the next 60 minutes. The volume and the free hydrochloric acid were determined for each period. A second histamine injection was given either after 30 or 60 minutes.

Results.—The effects of the simultaneous injections of histamine and histaminase are shown in Fig. 2, 3, 4, and 5. In Experiment 2, only 280 units of histaminase were injected, an amount which proved inadequate in preventing the response to histamine. This is in agreement with the conclusions of the earlier workers (3)

and (4) that small amounts of histaminase do not have action *in vivo*. In the experiments reported here the unit was approximately 15 times larger than the Winthrop unit used by earlier workers. Thus the amount of histaminase used in Exp. 2, for example, was at least 200 times higher than any dosage previously employed. Doses of histaminase varying from 500 to 1300 units were injected in Experiments 3, 4, and 5. Very marked or even complete inhibition of the histamine-induced activity of the gastric pouch was observed in all these experiments.

This finding can not be taken, however, as evidence of an *in vivo* reaction between histamine and histaminase. Toxic symptoms were present in the dogs receiving histaminase as evidenced by vomiting, defecation, urination, inability to stand, etc. In Exp. 5 pronounced ischemia of the mouth of the fistulous opening was noted.

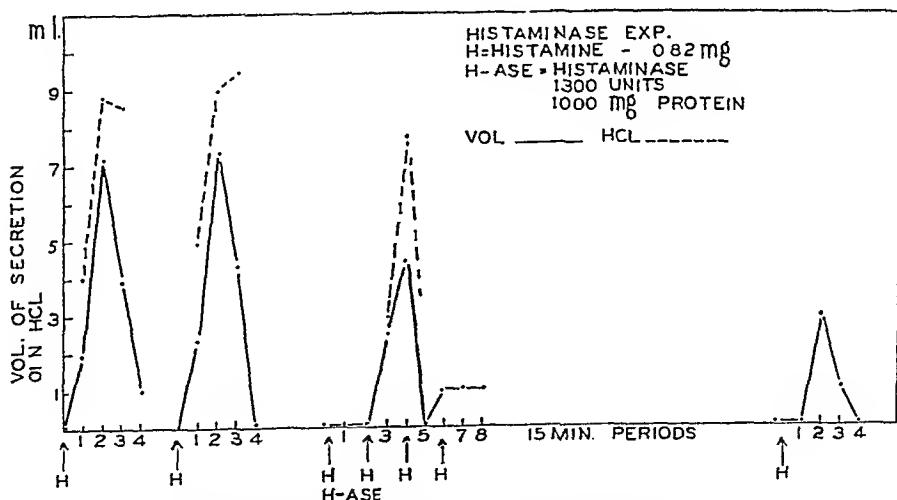


Fig. 5—Secretory response following the intravenous injection of 1300 units of histaminase and repeated subcutaneous injections of 0.82 mg histamine dihydrochloride.

The lack of the normal response to histamine in these experiments could have been caused, therefore, by the toxicity of the histaminase preparation. In order to test this hypothesis an active preparation of histaminase was

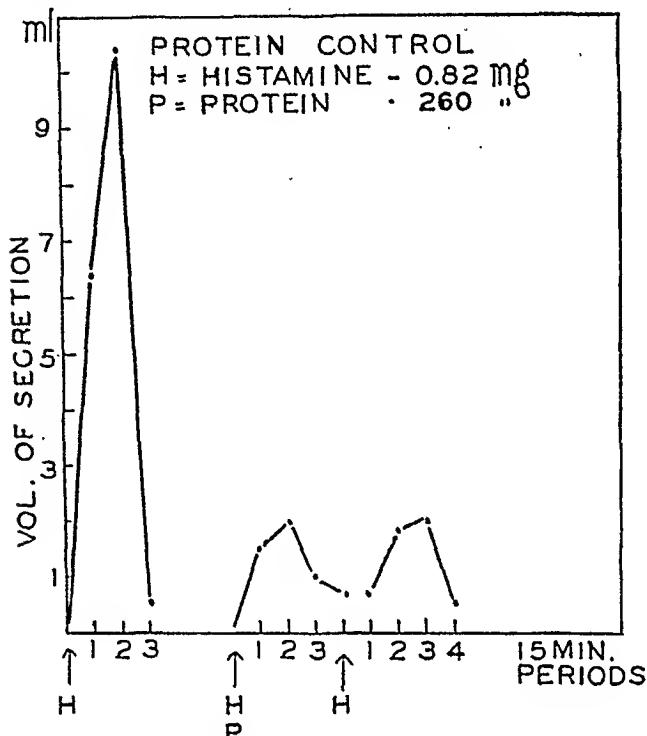


Fig. 6.—Secretory response following the intravenous injection of 260 mg of inactivated histaminase (containing less than 30 units) and repeated subcutaneous injections of 0.82 mg histamine dihydrochloride.

inactivated by exposure to pH 4.5 for one hour at room temperature. The denatured protein was centrifuged

off, and the pH of the supernatant readjusted to 7. Upon testing it was found to contain only 30 units of activity and 260 mg of protein. When this preparation was injected into a Heidenhain dog grave toxic symptoms were produced. There was almost no response to histamine (Fig. 6). The toxicity and gastric inhibition were more pronounced in this experiment than in Experiment 5, when a preparation of histaminase containing 1000 mg protein and having an activity of 1300 units was injected.

SUMMARY

Preparations of histaminase from hog kidney, having potencies of at least one unit per mg of protein were found to be highly toxic when injected intravenously into dogs in amounts above 300 mg. The toxicity apparently was not due to histaminase itself because a preparation of histaminase, which had been inactivated, was found to be even more toxic per mg of protein.

The toxic symptoms observed were trembling of extremities, coldness, ischemia of the gastric mucosa, vomiting, and defecation. This condition prevented normal activity of the gastric mucosa, and therefore made it impossible to use the inhibition of gastric secretion as an assay of the activity of histaminase *in vivo*, at least in the present state of purification of histaminase.

1. Laskowski, M., Lemley, J. M., and Keith, C. K.: Arch. Biochem. 1945, 6, 105.
2. Lemley, J. M., and Laskowski, M.: Arch. Biochem., ibid., 1945, 6, 115.
3. Necheles, H., and Olson, W. H.: Am. J. Dig. Dis., 1941, 8, 217.
4. Atkinson, A. J., Ivy, A. C., and Bass, V.: Am. J. Physiol., 1941, 132, 51.

Lymphosarcoma Of The Stomach

By

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THE differentiation of lymphosarcoma from other gastric lesions is important because of the possible efficacy of X-ray treatment in lymphosarcoma. X-rays may completely resolve a large lymphosarcoma of the stomach whereas a carcinoma of similar size would be correctly regarded as inoperable. The diagnosis of lymphosarcoma of the stomach is almost never made or even suspected during life without gastroscopy or exploratory laparotomy and biopsy. The purpose of this paper is to attempt to establish diagnostic criteria that may lead to the suspicion of lymphosarcoma early enough to be of more than academic interest.

Lymphosarcoma of the stomach is less difficult to diagnose when it is part of a systemic process. If the skin, the superficial lymph nodes, or the mucosal surfaces accessible to biopsy are involved, the diagnosis may be made by tissue examination. X-ray of the chest

may lead to the correct diagnosis when associated lymphosarcoma of the mediastinal lymph nodes occurs. A few positive clinical diagnoses of lymphosarcoma of the stomach have been made under these circumstances. Holmes, Dresser and Camp (1) diagnosed one case when gastric symptoms developed during the course of X-ray treatment of the superficial lymph nodes for lymphosarcoma. X-ray studies of the stomach revealed an irregular lesion in its lower third with absent peristalsis at the site of the lesion. Two weeks after X-ray therapy to the stomach, the irregularity had vanished, peristaltic waves passed over the previously affected area, and the symptoms disappeared. The inference was that the stomach lesion must have been lymphosarcomatous.

When the sarcomatous process is localized to the stomach, the diagnosis is far more difficult but also more important because amelioration or cure might be effected

by X-rays, whereas in a disseminated process the likelihood of complete cure is slight. Criteria for the diagnosis of localized lymphosarcoma of the stomach have not previously been developed because: (1) The disease is rare. (2) It mimics carcinoma or ulcer completely in the majority of cases. (3) The differential features seldom appear. (4) Some of these differential features occur also in atypical cases of carcinoma, gastritis, syphilis, and other diseases of the stomach. (5) The suggestive features may not occur until late in the disease. Ex-



Fig. 1—X-ray of 8/28/30. Lymphosarcoma of Stomach

ploratory operations done early may prevent the development of suggestive clues. This would be the cause of no regret if the problem were confined to operable cases. But in the apparently inoperable cases or in those simulating peptic ulcer amenable to medical treatment, the diagnosis is even more important because of the possible benefits of x-ray therapy. In these cases the diagnosis may not be made because the course of the disease has not been sufficiently analyzed.

The case here reported provides an opportunity for a study of the uninterrupted evolution of the disease from the onset of symptoms until death four years later.

Report of Case

A housewife, aged 58, had been ill for four years when she first consulted one of us (L. C.) November 16, 1934. Her sickness had begun with attacks of epigastric pain in 1930. A diagnosis of gall bladder disease was made at that time. This was apparently confirmed by non-visualization of the gall bladder when cholecystography was attempted. X-ray pictures of the stomach (Fig. 1) were regarded as normal. Cholecystectomy was advised but refused.

Severe, cramp-like, epigastric pains radiating to both upper abdominal quadrants led her to be hospitalized for diagnosis in November, 1931. The pains, present

for the preceding two years, lasted for three or four days and were at times followed by yellow sclerae and itching of the skin. Nausea and vomiting sometimes occurred during the attacks. The pain had no relation to meals but was occasionally relieved by soda or bowel movements. Between attacks pyrosis was frequent. Preceding the pain, abdominal distention, flatulence, and belching occurred. Constipation was marked. The stools were never tarry nor clay colored. The patient had lost 25 pounds although her appetite was fair. Vertigo bothered her occasionally. At this time she was well developed and well nourished but looked somewhat older than her stated age. Questionable icterus of the sclerae was observed. Marked excoriation of the back and shoulders was present. The liver, spleen and lymph nodes were not enlarged. The hemoglobin was 60%, with 5,600,000 red blood cells per cubic millimeter. The leukocyte count was 6400. Serological tests of the blood were negative. The urine contained no bile nor other pathological constituents. No free acid and 12° total acid were found in the stomach contents after an Ewald meal. The Graham-Cole test indicated good function of the gall bladder at this examination. A barium meal revealed a defect in the terminal antrum which did not fill well at any time. Intervals of hyperperistalsis and very deep cutting waves were present in the upper part of the stomach. They faded as they approached the defect. Emptying was good. The deformity persisted on three films. (Fig. 2a and 2b) Carcinoma of the pyloric end of the stomach and chronic cholecystitis were diagnosed. The patient



Fig. 2a—11/13/31. Lymphosarcoma of Stomach

again refused surgery.

Three months later the defect in the stomach was no longer seen. Peristaltic waves passed to the end of the antrum, the rugae were parallel and the pyloric ring was rather wide (Fig. 3). The Ewald meal now produced 6° free and 28° total acid. No blood was found in the stool. The blood count remained approximately normal. On the basis of these findings the diagnosis of carcinoma was deemed erroneous.

In October, 1934, X-ray examination again revealed a filling defect on the lesser curvature of the stomach. At this time, achlorhydria was present after an Ewald

meal. Although no blood was found in the stool, the X-ray appearance was regarded as diagnostic of carcinoma. Surgery was deferred because of an unexplained high fever.

November 18, 1934, the patient entered Mt. Sinai Hospital complaining of more or less constant pain radiating from both axillae to the epigastrium and the back, anorexia, weakness and occasional vomiting. Vertigo so severe that she could not raise her head from the pillow



Fig. 2b—Lymphosarcoma of Stomach

had been present for three days. In spite of her apathetic appearance, evidence of marked weight loss and muddy complexion she did not look acutely ill. The sclerae were not icteric. The right palpebral fissure was smaller than the left. Marked, prolonged, horizontal nystagmus was observed. The hearing was considerably diminished bilaterally. No lymphadenopathy was noted. The abdomen was soft. A deep, very tender mass with slight respiratory mobility and without bruit or thrill was palpated in the epigastrium. A soft, tender, cyst-like mass was ballotable in the right upper abdominal quadrant. It moved somewhat with respiration. The tip of the spleen was also felt.

The stool now contained occult blood and occasional red, white, and epithelial cells. The blood count and smear were still normal. The icterns index was 10 and the Van den Bergli test negative. The stomach contents, after an Ewald meal, contained no free and 20° total acid, a trace of lactic acid, many epithelial cells and white cells in clumps. The left side of the diaphragm was elevated to the level of the right in a chest x-ray. The gall bladder was not visualized when cholecystography was attempted. The stomach was deformed by irregular filling defects, especially of the greater curvature. The distance between the lesser curvature and the spine was increased as if by an interposed mass. The x-ray diagnosis was "inoperable cauliflower carcinoma of the stomach." (Fig. 4)

Fever first occurred on November 21 and continued until death. It became septic a week later with peaks

of 104°, chills and profuse sweats. Blood cultures and agglutination tests for typhoid, dysentery and melitisis were negative. No malaria parasites were found in blood smears. Dullness appeared over the left pulmonary base at this time. This, together with elevation of the left side of the diaphragm, pointed toward the presence of a subphrenic abscess.

The outstanding features of the case were: fever, a mass in the abdomen resembling Riedel's lobe, a spleen whose tip was just palpable at the costal margin, tenderness over an indistinct mass in the epigastrium, an irregular, poorly filled stomach with carcinoma-like termination of the defect at the pylorus, achlorhydria, occult blood in the stool, and non-visualization of the gall bladder.

The fever and enlarged spleen were regarded as not characteristic of carcinoma, nor did the patient look cachectic in spite of the loss of 25 pounds. Because of these inconsistencies mild antisiphilitic therapy was tried even in the absence of positive serological tests. The patient did not improve under the treatment.

Exploratory laparotomy was performed by Dr. H. M. Richter on December 15. He found a soft infiltration of the pylorus and antrum suggesting a granuloma rather than a carcinoma. The upper half of the stomach was involved to the diaphragm in a stony hard, irregular mass that seemed certainly to be an inoperable carcinoma. One of the many soft lymph



Fig. 3—Lymphosarcoma of Stomach

nodes along the gastric curvatures was removed for biopsy. The gall bladder was normal and contained no stones.

In the excised perigastric lymph node, the pathologist, Dr. Israel Davidsohn, found complete absence of

the normal structure. An infiltration of large mononuclear cells with pale, vesicular nuclei, prominent nucleoli, and a small amount of pink-staining cytoplasm had occurred. At the periphery of the specimen, atypical epithelial cells were found. The cells in the remainder of the node were extremely anaplastic.

The patient declined rapidly after the operation. Cough, expectoration, dyspnea, and rales appeared in both pulmonary bases. On December 21, superficial thrombophlebitis of the left leg was observed. X-ray treatment of the stomach was considered because of the peculiar, soft infiltration of its lower half and



Fig. 4—Lymphosarcoma of Stomach

because of the equivocal biopsy report, but the patient's high fever and poor condition precluded this. She died on December 29, 1934. The terminal events were bilateral bronchopneumonia, pulmonary edema, and multiple pulmonary infarcts from emboli originating from the thrombus in the left leg.

A primary reticulum cell sarcoma of the stomach was found at the necropsy performed by Dr. Israel Davidsohn. (Fig. 5) The stomach was densely adherent to the spleen. A lymphosarcomatous ulcer in the fundus of the stomach had perforated into the splenic vein. A second lymphosarcomatous ulcer was found on the anterior wall of the stomach. The heart, periaortic lymph nodes and adrenals were also infiltrated by the lymphosarcoma. The spleen was hyperplastic and contained multiple infarcts but no lymphosarcoma. Thrombosis had occurred in the splenic arteries and veins (Fig. 6). Bronchopneumonia and hemorrhagic infarcts were present in the lungs.

DISCUSSION

Pathogenesis. Lymphosarcomas may originate from any of the three types of cells found in lymphatic tissue: the lymphocyte, the reticulum cell whose processes from the meshes of the reticulum of lymph nodes, and the endothelial cell which lines the lymph sinuses and cavernous spaces. Distinct tumors which seem

to arise from each of these have been described as malignant lymphocytoma, reticulum cell (retothel) sarcoma, and endothelioma, respectively. The embryological relationship of these three types of cells is not clear. The morphology of the tumors arising from them is rarely so specific that derivatives of but one cell type are present. Usually a proliferation of all these cell types occurs in varying proportions so that classification is often difficult and arbitrary on the basis of the predominance of one or another kind of cell. This is especially true of the lymphocyte and reticulum cell tumors; the morphology of the endothelioma is usually distinctive. Some workers believe that reticulum cells may be transformed into lymphocytes while others think that these cell types are wholly distinct. Still others aver that the reticuloendothelial system is entirely separate from the lymphocytic system. They regard lymphatic leukemia, aleukemic lymphatic leukemia and lymphosarcoma as changes in the lymphatic system analogous to monocytic leukemia, aleukemic reticulosclerosis and reticular cell sarcoma in the reticuloendothelial system. Confusion is further increased by the participation of these same cellular elements in the inflammatory response to certain specific infectious agents such as those of tuberculosis, syphilis and typhoid fever as well as in Hodgkin's disease and the leukemias. This confusion is practically demonstrated in the difficulty of classifying the changes in lymph nodes removed for biopsy early in these diseases. Differentiation may be impossible between aleukemic leukemia, benign lymphocytoma, early lymphosarcoma, early "atypical" Hodgkin's disease and early retothel sarcoma. The diagnosis of benign lymphocytoma made in an early biopsy may be changed in later ones to

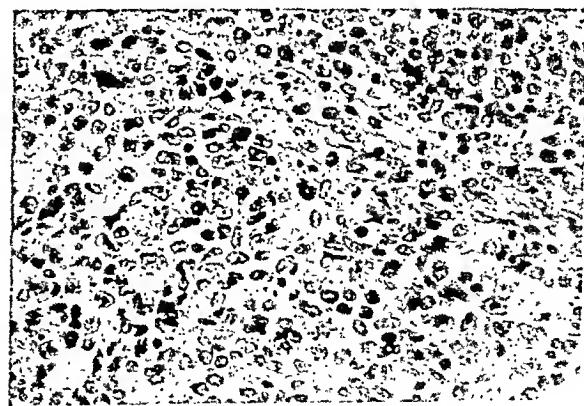


Fig. 5—Lymphosarcoma of Stomach

aleukemic leukemia or leukemia, to lymphosarcoma of the lymphatic or retothel type, or to Hodgkin's granuloma or Hodgkin's sarcoma.

The clinical picture in these various inflammatory and blastomatous diseases of the lymphatic system is so alike that the diagnosis is almost invariably based on microscopic examination of a blood or bone marrow smear or of an excised lymph node. Any of them may be characterized by weakness, anorexia, pruritus, sweating, fever, anemia, lymphadenopathy, splenomegaly,

and symptoms and signs of pressure from enlarged lymph nodes on important structures. The differentiation of these diseases from one another is so difficult that many authors beg the question by lumping all of them together under the common name of "lymphoblastoma" or "lymphoblastic process."

CLINICAL FEATURES

Many aspects of this case were atypical for carcinoma. While none of them singly or in combination could absolutely rule out carcinoma, they were sufficiently unusual to justify the suspicion that some other gastric lesion might be present.

DURATION OF DISEASE WITH ABSENCE OF CACHEXIA

The four year course of this disease without cachexia or severe anemia would be most uncommon in carcinoma.



Fig. 6—Lymphosarcoma of Stomach

ONSET

In gastric carcinoma, digestive symptoms frequently develop suddenly in patients who have had no previous complaints. Our patient had digestive disturbances for two years before definite evidence of stomach involvement was obtained.

FEVER

A high fever of unexplained origin is occasionally the presenting symptom in cancer of the stomach (2). Fever may also occur in association with perforating peptic ulcer and perigastritis or perigastric abscess. This patient's fever, toward the end of the illness, may have been to some extent a consequence of rupture of the lymphosarcomatous ulcer. Splenic thrombosis may have been another cause of her terminal fever. However, fever is common in all types of lymphoblastoma. The mere presence of a lymphosarcoma may be an adequate explanation of the fever just as the presence of Hodgkin's disease is an adequate cause for the intermittent Pel-Ebstein fever so frequently observed. Other causes for the fever such as typhoid, paratyphoid, melitensis, septicemia and malaria were ruled out by appropriate tests.

SPLENOmegaly

A palpable spleen is almost never present with carcinoma because cancer produces enlargement only of the organs directly involved by it and atrophy of all others. The spleen is rarely involved either in primary or metastatic carcinoma. Nor is splenomegaly common in localized sarcoma of the mature lymphocytic type. In the diffuse involvement of the reticuloendothelial system found in reticular sarcoma splenomegaly is common. In this patient the splenomegaly was a consequence of infarcts. The very presence of splenomegaly is sufficiently atypical in carcinoma to make the consideration of other diagnoses necessary.

Occult blood first appeared in the stool three years after a large filling defect had been noted in the stomach. This would be extremely uncommon in carcinoma. Carcinoma begins in the mucosa and is therefore likely to ulcerate early. Lymphosarcoma starts in the submucosa. It produces ulceration by pressure on the blood vessels in the submucosa with consequent interference with the mucosal blood supply. Ulceration is likely to occur late as it did in this case. Lymphosarcomatous ulcers are usually large because by the time ulceration occurs, extensive submucosal involvement has produced widespread interference with the mucosal circulation.

Multiple lesions in the gastro-intestinal tract associated with one or more stomach lesions may suggest the presence of lymphosarcoma. Our patient had no gastro-intestinal lesions outside the stomach.

Disappearance of a filling defect in the stomach between the roentgen examinations in November, 1931 and February, 1932 would be difficult to explain in the case of carcinoma. Lymphosarcoma, however, may be so radiosensitive that the irradiation incident to a diagnostic study may be sufficient to produce retrogression. Temporary spontaneous retrogression of a lymphosarcoma has been reported. (3) Either spontaneous or roentgen-induced improvement may have occurred in our patient.

Prominence of the rugae is frequent in lymphosarcoma. Infiltration of the submucosa makes the mucosal pattern more distinct.

Gastroscopy may enable the physician to make a pre-operative diagnosis of lymphosarcoma. Schindler (4), Renshaw (5), and Giere (6) have described gastroscopic pictures different from those of carcinoma, ulcer and hypertrophic gastritis. Our patient was too sick for gastroscopy by the time a lesion other than carcinoma was suspected, but in gastric lesions whose etiology is in doubt, gastroscopy should be performed.

Differential Diagnosis. Large stomach lesions of long duration may be a result of granulomas as well as of neoplasms.

Syphilis of the stomach is associated with positive serological tests in more than 90% of cases (7). A palpable epigastric mass is unusual in gastric syphilis but an enlarged spleen may be present. Emaciation is usually much more marked in syphilis of the stomach than it was in our patient because the syphilitic stomach is able to tolerate only a small amount of food at any

one time. No patient can eat often enough to maintain adequate nutrition under these circumstances. Our patient's repeatedly negative serological tests and her failure to respond to a therapeutic test with mercury and iodide made the diagnosis of syphilis untenable.

Other Chronic Granulomas. *Tuberculosis,* Hodgkin's disease and Boeck's sarcoid may produce large stomach ulcers. Exploratory laparotomy and biopsy are the only means of diagnosing them.

Chronic gastritis might be associated with x-ray findings similar to our patient's. The fever and the palpable spleen are not associated with gastritis. Differentiation of these conditions might be made by gastroscopy in some cases.

1. Holmes, G. W., Dresser, R., and Camp, J. D.: Radiology, 1926, 7, 44.
2. Singer, H. A., and Steigmann, F.: Am. J. Dig. Dis. and Nutri., 1936, 3, 731.
3. Longcope, W.: Bull. Ayer Clin. Lab., 1910, 6, 1.

REFERENCES

4. Schindler, R.: Gastroscopy, University of Chicago Press, 1937, 260.
5. Renshaw, J. F.: J. Am. Med. Assn., 1936, 107, 426.
6. Giere, C. N.: J. Am. Med. Assn., 1941, 117, 173.
7. Eusterman, G. B.: J. Am. Med. Assn., 1931, 96, 173.

Carcinoma Of The Esophagus

*Transpleural Resection and Esophago-Gastrostomy**

By

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UNTIL quite recently, the surgical treatment of carcinoma of the esophagus was entirely palliative and consisted either of gastrostomy or jejunostomy and had for its purpose the relief of obstructive disturbances and the feeding of the patient. However, as a result of the development of new techniques and with the earlier recognition of the disease in its operable stage, the surgical treatment has become directed toward the actual eradication of the lesion proper. In this country, the first successful resection of the esophagus for carcinoma was performed by F. Toreck (1). In this operation, the distal portion of the esophagus, after the carcinomatous portion had been resected, was closed and the proximal portion was brought out upon the skin forming a permanent stoma at this site. The first case in this country in which the continuity of the esophagus and stomach was re-established, by performing an esophago-gastrostomy after resecting the carcinomatous portion of the esophagus, was performed by W. E. Adams and D. B. Phemister (2). Since then there have been more reports of such successful operations, J. Garlock (3), E. D. Churchill and R. H. Sweet (4) have reported comparatively large series of such cases. H. Lillenthal (5) was one of the pioneer workers in this field and reported a successful case in which the operation was performed by the extrapleural posterior mediastinal

approach. In the other reports noted above, the operation was performed by the transpleural transdiaphragmatic method.

It is not only significant but it is also clinically important to realize that carcinoma of the esophagus remains a localized disease for a considerable time and metastasizes quite late in the course of the disease. In a series of postmortem examinations, Watson (6) found an absence of metastatic lesions in 50% of his cases Helsley (7) encountered similar findings in 64% of his autopsy cases and Zuppinger (8) found that 33% of his postmortem examinations showed an absence of metastases. Keeping these figures in mind and noting that 3½% of all deaths from cancer in New York City can be attributed to carcinoma of the esophagus, Watson (6), it is quite obvious that early diagnosis would change the nature of treatment of this disease from merely palliative to truly radical with a corresponding change in the end results. The following case is reported to demonstrate what can be accomplished by radical treatment in these cases even when the condition appears to have reached the stage of inoperability.

CASE REPORT

C. P. #116329 male 62 years old was admitted to City Hospital, New York City, July 30th, 1942. His family and past history were irrelevant and have no bearing upon his present condition. Up to about nine months ago the patient felt perfectly well. At

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SUMMARY AND CONCLUSIONS

Far advanced caniflower carcinoma of the stomach had been diagnosed by roentgen examination of the subject of this case report. The four year duration of the disease without cachexia, the prolonged septic fever, the splenomegaly and the late appearance of occult blood in the stool led to the speculation that a lymphoblastoma might be present. This was confirmed by necropsy.

The occurrence of these clinical features, separately or in combination, should lead to the suspicion of lymphoblastoma of the stomach. Appropriate diagnostic measures including gastroscopy and a trial of X-ray therapy should be instituted as soon as possible in such cases.

that time he began to vomit solid foods almost immediately after eating. Shortly thereafter, he began to vomit semi-solid foods and at the present time he is having considerable difficulty in swallowing and retaining fluids. During this time he has had almost continuous epigastric distress. There has been a weight loss of 40 pounds and he has become quite asthenic. Just before admission to this hospital, he was investigated at the Columbus Hospital, New York City, where a diagnosis of carcinoma of the stomach was made.

Physical examination shows the patient to be markedly cachectic. The abdomen is scaphoid, the skin is loose and wrinkled with almost complete loss of subcutaneous fat. No other abnormalities were noted. Clinical impression—carcinoma of the lower esophagus or of the cardia of the stomach. On August 3rd, 1942 a barium Roentgenogram of the esophagus was taken. The report reads as follows: "A study of the esophagus with barium reveals an irregular filling defect involving the distal end, with some dilatation above this lesion with constriction. The above findings indicate an organic lesion. This is most likely a carcinoma."

In view of the marked asthenia and cachexia, a radical surgical procedure at this time could not be carried out safely. A jejunostomy was planned as a preliminary operation with the idea of (1) overcoming the marked undernourishment and starvation by the introduction of a high caloric diet directly into the intestines and (2) of putting the esophageal lesion at complete physiologic rest and thus reducing the secondary inflammation which invariably accompanies an ulcerating carcinomatous lesion.

On August 7, 1942, a jejunostomy was performed. The stomach and the distal portion of the esophagus were palpated at this time. The abdominal portion of the esophagus was found to be markedly indurated, thickened and fixed. The lymph nodes in the gastro-hepatic omentum near the cardia were enlarged and quite hard. The patient made an uneventful postoperative recovery and picked up rapidly with the high caloric jejunostomy feedings and blood transfusions. By August 24, 1942, his general condition had improved to such an extent that a radical excision of the carcinoma could be done.

Pre-operative diagnosis, Carcinoma of the lower third of the esophagus.

Post-operative diagnosis, Same.

Operation Transthoracic and Transdiaphragmatic Resection of the lower third of the esophagus and of the cardia of the stomach with primary esophago-gastrostomy.

Findings. Lower third of the esophagus was firmly attached to the surrounding structures. Clump of hard fixed lymph nodes in the gastro-hepatic ligament near the cardia about the size of walnut.

PROCEDURE

With the patient lying on his right side, an incision was made in the left seventh interspace from

the mammary line anteriorly to a point midway between the line of the angle of the scapula and the vertebral bodies, posteriorly. Segments, $\frac{3}{4}$ inch in length were removed subperiosteally from the seventh and eighth ribs near the posterior angle. The pleural cavity was now opened through the seventh intercostal space. The wound was retracted widely and very satisfactory exposure of the pleural contents was obtained. The lung was now covered with warm pads and retracted leaving the mediastinal structures and the diaphragm in full view. The movements of the diaphragm were now quieted by crushing the phrenic nerve. The mediastinal pleura above the neoplasm was incised longitudinally and this part of the normal esophagus was freed from the surrounding structures by blunt dissection. The dissection was now carried down toward the diaphragm freeing the organ to the hiatus. At this point the adhesions were so dense that it was necessary to cut the diaphragm radially from the esophagus toward the chest wall for a distance of five inches in order to continue with the dissection of this structure from the abdomen. With this maneuver the freeing of the neoplasm became comparatively simple. The superior portion of the gastro-splenic ligament was ligated and cut. The left portion of the gastrohepatic ligament and the gastric artery were now ligated and severed. The cardiac portion of the stomach was thus mobilized and could be readily brought up into the pleural cavity. A rubber covered clamp was now placed across the esophagus about two inches above the upper part of the neoplasm. A similar clamp was placed across the stomach about two inches below the lower part of the tumor. The neoplasm was now removed with a normal zone of esophagus above and with the cardia of the stomach below. The opening in the stomach was closed with two layers of sutures thus forming a closed upper pouch. The free end of the remaining esophagus was now anastomosed to the gastric pouch making the union on the anterior wall of the stomach about one inch below the blind upper extremity. The esophago-gastrostomy was of the end to side variety employing the customary two layers of sutures. The inner layer of sutures was interrupted throughout in order to avoid the possibility of stricture formation at the site of the anastomosis, which is much more apt to occur when a continuous suture is used. In order to avoid drag and tension on the suture line as a result of movements of the adjacent viscera, several interrupted sutures were placed through the sides of the gastric pouch attaching it firmly to the adjacent parietal pleura and endothoracic fascia. In this manner, the possibility of a leak at the site of the suture line is reduced to a minimum. The inner portion of the incised diaphragm was now closed by sewing it to the stomach about an inch below the line of anastomosis. The outer portion was closed with a continuous catgut suture. A second layer of sutures was applied to assure an effective closure. The chest wall proper was now closed by applying three stout

pericostal chromic gut sutures. The muscle layer was brought together with a series of closely applied catgut sutures to assure an airtight closure of the chest wall. The fascia was united in a similar fashion. The skin proper was closed with a layer of interrupted silk sutures. Before closure of the chest wall was begun, an opening was made in the ninth intercostal space posterior axillary line and a mushroom catheter was introduced into the pleural cavity for drainage. This catheter was in turn attached to a tube that was placed under water thus producing under water negative pressure.

* * * * *

Pathologic Report. Dr. J. R. Lisa, Pathologist.

Specimen submitted consists of portion of esophagus and stomach in one mass, as well as a small mass of lymph nodes. Esophagus portion measures 5 cm. in length and 3 cm. in width. Resected portion of stomach measures 4 cm. by 7 cm. The wall of the esophagus is markedly thickened and extremely hard. The mucosa is ulcerated. The ulcerated portion extends to the point of junction of esophageal gastric mucosa. The large hard nodule measures 2.5 cm. in its greatest diameter, is firmly adherent to the outer wall of the esophagus at the same level where ulceration is noted within the esophageal mucosa. The mass of lymph nodes measures 3.5 cm. by 1.5 cm. by 1 cm. The nodes are small and hard in consistency.

Microscopic examination. Sections examined reveal numerous small and large irregular solid cords of squamous epithelial cells invading the muscular coat of the esophagus and extending to the areolar tissue about the wall. Many horny pearls are noted in the cords. Similar epithelial cords are noted in the lymph nodes.

DIAGNOSIS

Squamous cell carcinoma with metastases to lymph nodes. Post-operative course. September 2, 1942. Except for a partial atelectasis of the left lower lobe, the post-operative course was uneventful. The temperature at this time rose to 104 and dropped to normal synchronously with the spontaneous expansion of the collapsed lung. There was a small amount of blood stained serous discharge from the drainage tube during the first three days after which the drainage was discontinued. The wound proper healed by primary union. The patient was now taking fluids by mouth and was showing a slow but steady improvement. Some two days later, he was able to take small quantities

of soft food. Three weeks after the resection, he was eating fairly large amounts of semi-solids including meat loaf and string beans. Feedings by way of the jejunostomy tube had been discontinued two weeks after operation. After a few days, the patient was put on a regular diet. A barium x-ray of his esophagus and stomach taken at this time showed a satisfactory re-establishment of the lumen at the site of anastomosis. He had no complaints of any kind and was thriving most satisfactorily both in weight and strength. He was discharged on September 19, 1942 and referred to the surgical follow-up clinic for further observation.

Final follow-up note.

On March 12, 1943, the patient developed a right lower lobe bronch-pneumonia that cleared up spontaneously. He was feeling quite well up to May 11, 1943, when he began to notice the same difficulty in swallowing solid food, that he had when he first sought medical help. A Barium X-ray was taken at this time and a marked narrowing was noted at the lower end of the esophagus with a dilatation above it. On May 27, 1943, a palliative jejunostomy was performed. The general condition of the patient deteriorated steadily and some two months later, July 25, 1943, the patient died. The autopsy showed recurrent carcinoma at the site of the anastomosis with extension into the pericardium, pleura, peritoneum and abdominal lymph nodes.

SUMMARY

The findings at the time of operation showed the lesion to be no longer a local one, and thus, strictly speaking, was not an operative case. The disease had not only spread to the immediate surrounding structures but had already passed on to the lymphatic system. In view however of his extreme suffering and of the otherwise hopeless outlook, it was decided to attempt a radical surgical cure. For a period of nine months, the patient was able to work, and was free from disability. He was able to live a perfectly normal life during this time. When one considers the fact that this patient was treated for a period of nine months (from the time his symptoms had become fairly characteristic of this lesion to the time he was admitted to the hospital for operation), it is only fair to assume that the result would have been a much different and happier one if the surgical procedure could have been applied at the beginning of this period. In other words, in this disease as in others of similar nature, the important and essential factor is early diagnosis.

REFERENCES

1. Toreck, F.: *Surg. Gyn. & Obst.* vol. 16, p. 614, 1913.
2. Adams, W. E., and Phemister, D. B.: *Jour. Thor. Surg.* vol. 7, p. 521, 1938.
3. Garlock, J.: *Surg. Gyn. & Obst.* vol. 70, p. 556, 1940.
4. Churchill, E. D., and Sweet, R. H.: *Annals of Surgery*, vol. 115, p. 897, 1942.
5. Lilienthal, H.: *Annals of Surgery*, vol. 74, p. 116, 1921.
6. Watson, W. L.: *Surg. Gyn. & Obst.* vol. 56, p. 884, 1933.
N. Y. S. Jour. Med. vol. 36, p. 1615, 1936.
7. Helsley, G. F.: *Annals of Surgery*, vol. 77, p. 272, 1923.
8. Zuppinger, A.: *Ergeb. d. med. Strahlenforsch.* vol. 7, p. 389, 1936.

An Unusual Clinical Syndrome Following Ingestion Of Fish

By

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In November 1944 there was observed a clinical syndrome resembling that previously described as "fish poisoning" involving thirteen soldiers and two civilians stationed in Puerto Rico. The symptoms were rather unusual in that gastro-intestinal manifestations were mild except for one case in which they were moderately severe, whereas neurological involvement was quite prominent and was the cause of subjective complaints.

The type of fish involved in the various cases of poisoning has been confined to a small number of species and according to Gilman (1) the following have been reported as poisonous at one time or another in this area.

I CARANGIDAE (Jacks)

- | | |
|-----------------------------|------------------------|
| Amberjack..... | a. Seriola falcata |
| Yellowjack..... | b. Caranx bartholomaei |
| Skipjack or cavalla..... | c. Caranx ruber |
| Horse-eyed Jack, jurel..... | d. Caranx latus |

II SCOMBRIDAE (Mackerel)

- | | |
|---|--------------------------|
| Kingfish or sierra (cera) or
pintado | a. Scomberomorus cavalla |
|---|--------------------------|

III SPHYRAENIDAE

- | | |
|--------------------------------|---------------------------|
| Barracuda (large variety)..... | a. Sphyraenidae barracuda |
|--------------------------------|---------------------------|

IV LUTIANIDAE

- | | |
|------------------|-----------------|
| Red snapper..... | a. Lutianus aya |
|------------------|-----------------|

Outbreaks of fish poisoning have occurred almost every year among the native populations of Puerto Rico, Jamaica, the Virgin Islands, Cuba and Barbados, and the probability is that the actual number of cases far exceeds the number reported.

O'Neill (2) reported an outbreak of fish poisoning caused by a female amberjack (*Seriola fasciata*) which was caught near Culebra, adjacent to Puerto Rico. The fish had been pronounced as edible and was refrigerated less than one hour after death. Despite the fact that the fish was baked in an oven for over two hours before serving, all of the persons with one exception, eating the fish became ill.

Walker (3) described a number of cases which occurred from 1918-1921 in the region of St. Thomas. Most of the fish responsible for the outbreaks belonged to the "Carangidae" or "Jacks", and a lesser number were kingfish and barracuda; they were all caught in deep sea pots and were of large size.

Most of the cases reported have occurred in the late summer usually about September or during the fall and winter months, and until Gilman's report of ten cases which occurred in May, only an occasional case had been noted between March and August. The series of cases which is reported here, fits in very well with

the facts observed.

Thus far, no definite organism or toxin has been isolated. The possibility of bacterial origin cannot be dismissed, especially in view of the fact that stool cultures have not been performed but the consensus of opinion, in view of all the available facts, favors the theory of an endogenous toxin. Supporting the latter theory are the seasonal incidence, geographic distribution, the fact that only the larger species of fish become poisonous and then usually at the time of spawning, paresthesias of the tongue, mouth and hands, cutaneous itching and evidence that the causative factor is not destroyed by cooking.

Gilman raises an interesting point in connection with this: He states, "The problem varies directly not only with the amount of fishing done but with the more complete utilization of fishing as an essential industry in providing food for local consumption. Were certain fish known to be poisonous at all times the problem would have considerable less interest. However, the fact that certain fish of recognized food value and popularity may only occasionally prove to be poisonous is worthy and necessary of investigation."

The following case reports involve thirteen soldiers and two civilians who ate fish at the noonday meal. The fish was obtained from the commissary and was listed as "local assorted issue"; namely, it was caught in local waters and consisted of an assortment of different types among which were amberjack, kingfish, and red snapper.

The fish involved were improperly prepared prior to serving since they were kept exposed in a container of water at room temperature for almost twenty hours; bacterial growth would be possible under such circumstances.

At the meal in which the fish was served, there were approximately thirty-five men. However, only fourteen men ate the fish and thirteen of these fourteen became ill. In addition, two civilian KP's ate the fish and both of these men became sick.

The symptoms appeared within two to four hours after eating and agreed in many respects with those described by previous observers. They included:

a) Nausea, diarrhea and a distinct metallic taste in the mouth. b) Tingling sensation of the skin, itching, burning of the tongue and lips accentuated when drinking cold liquids. Paresthesias of the upper and lower extremities, weakness of the legs, severe muscular aches most marked in the extremities.

c) Nervousness, restlessness, insomnia, burning upon urination, and frequent micturition.

The cases are summarized in table I. The following illustrates some of the cases in more detail: (selected at random).

CASE REPORTS

Case No. 1

A 30 year old white male reported to the dispensary complaining of nausea, several loose stools, aching of the muscles of his extremities, itching of his skin and burning of his tongue. His diarrhea began two hours after a noonday meal in which fish was served; the remaining complaints began shortly thereafter. The next day he stated his skin felt as if someone were "sticking pins into him."

Physical examination revealed nothing significant except for slightly depressed knee jerks. Urinalysis was negative.

Case No. 2

A 28 year old white male came to the dispensary because of nausea, diarrhea, muscle aches and pains, tingling of his skin, weakness and burning of his tongue. The symptoms began three hours following the noonday meal in which fish was served. On the next day he began to complain of burning on urination but urinalysis was negative.

Physical examination revealed nothing significant.

Case No. 3

A 27 year old white male became ill about two and one half hours after eating his lunch which included a serving of fish. His complaints were 6-7 loose stools, muscle aches and pains, marked weakness, a metallic taste, burning of his tongue and lips, and prickly sensations of his hands and feet.

Physical examination did not reveal any unusual finding other than depressed patellar reflexes.

Case No. 4

A 31 year old white male became ill 4 hours after eating his noonday meal. He complained of nausea, diarrhea, followed by weakness, anorexia, metallic taste, muscular aching, burning of his tongue and lips upon drinking cold water and tingling of his hands when touching any cold object.

Physical examination revealed no abnormal findings except depressed knee jerks.

Case No. 5

A 25 year old white male complained of epigastric pain and nausea three hours after eating his noonday meal in which the main course was fish. Shortly thereafter, he began to experience a rather severe episode of diarrhea, passing seventeen loose stools during the next twenty-four hours. On the next morning he stated that he felt severe generalized aches and pains, a metallic taste, marked burning of his tongue when he drank cold water, tingling of his fingers upon handling cold objects, and itching of his skin. His muscular aches and pains persisted intermittently for more than one month.

Examination revealed generalized abdominal tenderness, but otherwise was negative.

Case No. 6

A 35 year old white male ate a helping of fish at lunch and two hours later, he became ill complaining of diarrhea. On the next day, he stated that his muscles ached, his legs felt weak, and he felt a burning of his tongue when drinking cold water. He had a

prickling sensation of his fingers and toes, accentuated when handling cold objects.

Physical examination revealed depressed knee jerks.

Served with the fish, which was baked, there was Spanish sauce consisting of onions, green peppers and salt and pepper. However there were many soldiers who partook of the sauce and not of the fish; none of these men became ill.

There were several dogs who ate leftovers from this noonday meal. Of four dogs, only one ate the fish and one hour thereafter became violently ill with profuse diarrhea and marked weakness. On the next day he could hardly stand and there was no improvement after a week at which time he was turned over to the laboratory for further observation and study. There he was treated with subcutaneous fluids and large doses of thiamine chloride. Stool cultures failed to reveal any causative organism, these cultures being taken at the laboratory while symptoms of gastro-intestinal involvement were still acute. Improvement was slow and the animal made an uneventful recovery.

In most of the cases the recovery time was prolonged. Several of the soldiers were well in two weeks but in others, the recovery was not complete for almost two months. The average time for recovery was approximately three weeks.

Treatment of all the cases was largely symptomatic and included analgesics for pain, large doses of thiamine chloride, calcium gluconate, tincture of belladonna and bismuth and paregoric in the more severe diarrheas.

The theory that the cases of fish poisoning are really cases of intoxication from fish spoilage cannot be ruled out completely; however evidence against this is the fact that most cases of similar fish poisoning reported in the literature occurred after the ingestion of fresh fish or fish that had been refrigerated immediately.

Up to the present time there has not been any toxin identified which could account for the different outbreaks, although as cases continue to be seen the evidence for a toxin being the causative agent becomes more convincing.

Pathological studies have not been performed since there have not been any deaths recorded so far. Owing to technical difficulties, we have been unable to perform blood and urine studies for thiamine values but in view of the fact that several men were not helped by large daily intravenous doses of thiamine chloride (50 mg) it is unlikely that the symptoms were due to an acute destruction of thiamine in the body. There have been sporadic cases among the native population but this is the first report occurring in army personnel in this area. It is hoped that as similar cases occur, they will be reported so that a truer incidence of this kind of poisoning will be appreciated. Furthermore, increasing numbers of feeding experiments should be done with specimens of fish to determine toxic effects in animals and many more studies are necessary to determine the chemical nature of this toxin.

It is advised that the species of fish involved in the various outbreaks of food poisoning be avoided during certain seasons when caught in waters around Puerto Rico and the Virgin Islands until further investigation

has disclosed more factual knowledge regarding the etiologic agent.

SUMMARY

1. A clinical syndrome resembling that previously described as "fish poisoning" was observed in thirteen soldiers stationed in Puerto Rico and two civilians who were working in the mess hall where the troops ate.
2. The chief complaints were nausea, weakness, numbness of the legs, diarrhea, paresthesias, metallic taste, cutaneous itching and muscular aches and pains. The paresthesias consisted of burning and tingling of

the tongue, mouth and lips, aggravated when drinking anything cold; in addition, there was a feeling of "pin pricks" in the fingers and toes. Symptoms occurred several hours after eating the fish. Recovery was slow and was complete in three weeks in the average case.

3. Treatment was symptomatic and consisted of analgesics for pain, thiamine chloride, calcium gluconate, tincture of belladonna and bismuth and paregoric in the more severe diarrheas.

4. The causative agent, most likely a toxin calls for further investigation. This toxin occurs in certain species of fish caught in the waters adjacent to Puerto

TABLE No. 1

Case No.	Symptoms	Positive Findings on Physical Examination	Treatment	Recovery Time
1	Nausea; Diarrhea; generalized muscular aches more marked in extremities, burning of tongue; numbness in legs; frequent micturition.	Slightly depressed knee jerks.	Acetylsalicylic acid; milk of magnesia; thiamine chloride orally 3 mg t.i.d. for one week.	15 days
2	Diarrhea; nausea; weakness; severe pains in upper and lower extremities; headache; metallic taste; cutaneous itching.	No significant findings.	Tincture of belladonna; acetylsalicylic acid; thiamine chloride orally 3 mg t.i.d.	3 weeks
3	Diarrhea; nausea; burning of tongue; weakness; metallic taste; paresthesias of hands and feet; insomnia.	No significant findings.	Milk of magnesia; acetylsalicylic acid; bismuth and paregoric; thiamine chloride orally 3 mg t.i.d.	4 weeks
4	Diarrhea; metallic taste; burning of tongue and lips; paresthesias; muscular aches and pains; weakness; cutaneous itching; dysuria.	No significant findings.	Bismuth and paregoric; tincture of belladonna; thiamine chloride orally 3 mg t.i.d.	5 weeks
5	Diarrhea; epigastric pain; vomiting; metallic taste; burning of tongue; paresthesias of hands and feet; severe muscular aches; sweating; frequent micturition.	Depressed knee jerks; generalized abdominal soreness.	Bismuth and paregoric; tincture of belladonna; 50 mg thiamine chloride intravenously daily for 5 days. 15 gr calcium gluconate intravenously daily for 2 days.	6 weeks
6	Epigastric pain; nausea; diarrhea; muscular aches; burning of tongue; paresthesias of hands, forearms and legs.	Depressed knee jerks; abdominal tenderness generalized.	Tincture of belladonna; acetylsalicylic acid. Thiamine chloride 3 mg t.i.d.	3 weeks
7	Diarrhea; nausea; anorexia; muscular pains; burning of tongue; metallic taste; numbness of legs and feet; insomnia; cutaneous itching.	No significant findings.	Tincture of belladonna; milk of magnesia; thiamine chloride 3 mg t.i.d.	3 weeks
8	Nausea, abdominal discomfort, diarrhea; paresthesias; muscular aches; burning of tongue; metallic taste; itching of skin.	Depressed knee jerks; slight abdominal soreness.	Bismuth and paregoric; thiamine chloride 3 mg t.i.d.	4 weeks
9	Nausea; vomiting; diarrhea; epigastric pain; severe muscular aches in upper and lower extremities, burning of tongue and lips; paresthesias; burning on urination.	Slight abdominal soreness; depressed knee jerks.	Bismuth and paregoric; tincture of belladonna; acetylsalicylic acid; thiamine chloride 50 mg daily intravenously for 5 days; calcium gluconate 15 grains intravenously daily for 5 days.	6 weeks
10	Nausea; slight epigastric discomfort; diarrhea; burning of tongue; paresthesias; metallic taste; numbness of feet and legs.	No significant findings.	Bismuth and paregoric; tincture of belladonna; thiamine chloride 3 mg t.i.d.	10 days
11	Burning of tongue; weakness; paresthesias, muscular aches; metallic taste; itching of skin.	Depressed knee jerks.	Thiamine chloride 3 mg t.i.d.	3 weeks
12	Diarrhea; metallic taste; burning of tongue; paresthesias; muscular aches; weakness; anorexia; insomnia; restlessness.	No significant findings.	Tincture of belladonna; thiamine chloride 50 mg intravenously daily for 4 days	3 weeks
13	Diarrhea; weakness; anorexia; headaches; muscular aches and pains; paresthesias of hands and feet; cutaneous itching.	No significant findings.	Bismuth and paregoric; tincture of belladonna; thiamine chloride 3 mg t.i.d.	2 weeks
14	Diarrhea; anorexia; weakness; burning of tongue; paresthesias; metallic taste; muscle cramps in legs and thighs.	Depressed knee jerks.	Milk of magnesia; tincture of belladonna; thiamine chloride 3 mg t.i.d.	3 weeks
15	Epigastric discomfort; paresthesias; metallic taste; burning of tongue; weakness; anorexia; insomnia; frequent voiding.	No significant findings.	Tincture of belladonna; thiamine chloride 3 mg t.i.d.	10 days

Rico and the Virgin Islands, is more common at the time of spawning and is not destroyed by heat or refrigeration.

5. This is the first outbreak of its kind among army personnel, although sporadic cases have occurred among the native population.

6. It is hoped that as many cases as possible be

reported so that a truer incidence of this type of fish poisoning will be appreciated.

7. It is advised that pending further investigation, the species of fish which have been involved in the outbreaks of fish poisoning be declared unsafe for human consumption during certain seasons of the year when caught in waters around Puerto Rico and the Virgin Islands.

REFERENCES

1. Gilman, Robert L.: A Review of Fish Poisoning in the Puerto Rico-Virgin Islands Area. A Report of Ten Cases Occurring on Culebra Island, U. S. Nav. Med. Bull. 40: 19-27. January 1942.
2. O'Neill, J. B.: Food Poisoning in the First Marine Brigade, Fleet Marine Force, Culebra, P. R. U. S. Nav. Med. Bull., 36:629-631; October 1938.
3. Walker, F. D.: Fish Poisoning in the Virgin Islands. U. S. Nav. Med. Bull., 17:193-202; August 1922.

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MOUTH AND ESOPHAGUS

SEASE, C. I.: Parotid duct fistula. Report of a case with a simple method of treatment. *Virginia Med. monthly*, v. 72, p. 217, May 1945).

A parotid duct fistula developed in a patient as the result of removal of a cyst of the parotid gland. Treatment was as follows: Stenson's duct was dilated with small probes. Silkworm gut was passed thru the fistula, the end knotted and drawn into the wound so that the knot stayed in the wound. The fistula was then closed. A week later the knot was pulled out. The fistula had closed and has remained closed for the past twenty years since the operation.—G. N. Smith.

ZISKIN, D. E., LOUGHLIN, W. C. AND SIEGEL, E. H. Diabetes in relation to certain oral and systemic problems. A histological study of the gingivae and oral mucous membranes. *Am. J. Orthodont. Oral Surg.*, v. 30, p. 758, 1944).

Fourteen juvenile and 5 adult diabetics, all insulin treated and 2 diet-controlled diabetics were studied. Insulin-treated cases showed hyperkeratinization, hyperplasia of epithelium and of connective tissue, increased glycogen deposits, fibroblasts and prominence of the capillary bed, and reduction of inflammatory exudate. These changes constituted variations from the normal. Diet-controlled cases also showed hyperkeratinization in contrast to the normal. Evidence of degenerative and inflammatory changes was attributed to the nutri-

tional and metabolic status. Four normal rhesus monkeys were studied for the systemic and local gingival effects of insulin. Insulin was injected parenterally into two and applied topically to the gingivae of two others. The latter showed the same slight changes as the injected monkeys. This was attributed to the systemic effect of the absorbed insulin. Additional hyperkeratinization was seen in that region of the gums where the insulin was applied, and was attributed to local application. The hyperkeratinization in these areas was greater in amount than in those considered to be of systemic origin. The areas of application also disclosed a noteworthy increase in the glycogen content of the gingivae. These changes emphasize the benefits of the topical application when such results are desired. The high incidence of suboptimal vitamin A plasma level in diabetics is presented as a possible factor in the production of the changes seen in the gingivae. It is suggested that insulin itself as well as the diabetes may be an agent creating a metabolic disturbance in the cells of the gingivae. The deposition of an increased amount of glycogen in the gingivae in the insulin-treated diabetics and in the monkeys receiving insulin topically is of especial interest but of unknown import. The changes shown in the subjects, their violaceous coloration, thickening, hyperkeratinization, decrease in inflammatory exudate and increase in glycogen deposition, may be of a protective nature.—Biological Abstracts.

CLINICAL MEDICINE
BOWEL

BARBOSA, J. DE C., BARGEN, I. A. AND DIXON, C. F.: *Regional segmental colitis.* (*Proceed. Staff Meet. Mayo Clinic*, v. 20, p. 134, May 2, 1945).

The term "chronic ulcerative colitis" refers to a group of different disease entities among which group is included "segmental" or "regional" colitis. Regional colitis refers to a "nonspecific or cryptogenic inflammatory ulcerative or hyperplastic lesion involving one or more short or long segments of large bowel." The terminal portion of the bowel is spared. The lesion may be continuous or consist of multiple involvements. The ileum is either not involved at all or is involved secondary to the main colonic lesion. At the Mayo Clinic segmental colitis constituted four per cent of all cases of ulcerative colitis. The oldest patient was 73 years, the youngest three years and the sex distribution was equal.

The origin of the regional colitis still remains unknown. All experiments on the subject have yielded either negative or dubious results.

The authors discuss the characteristic lesions they found in their series of patients coming to surgery and present an outline of the clinical course of the patient. They advocate medical treatment of some sort for most patients. Rest, proper diet, supportive measures including blood transfusions are recommended. If surgery is advisable, then radical operation is the best treatment. The authors emphasize that it is essential to resect the bowel well beyond the apparent limitation of the disease. Although roentgenographic studies appear to show a sharp demarcation line, and direct examination at operation may likewise reveal a sharp limitation area, careful inspection will reveal extension of the disease processes for 4 to 6 inches beyond. Stippling of the serosa without thickening of the bowel, due to minute punctate hemorrhages, is found distal to the involved area. The stippled segment must also be removed or recurrence will ensue. The reason for the spread of the regional colitis disturbance is not known: it appears to be due to direct extension and not to spread by the lymph vessels.—F. X. Chockley.

PHILIPSBORN, H. F., LAURENCE, G., GIBSON, S., AND GREENGARD, H.: *Analysis of duodenal drainage in celiac syndrome.* (*J. Pediat.*, v. 26, p. 107, Feb., 1945)

Since the stools in celiac syndrome and pancreatic insufficiency may be identical in appearance and chemistry and the vitamin A absorption curves are non-specific, some other method of differentiation must be sought. Duodenal intubation and stimulation with secretin was done in the usual manner. Tryptic activity was measured by the Northrop-Kunitz method. Amylase was determined by Wohlgemuth's method. Lipolytic activity was determined by the method of Cherry and Crandall. Value for tryptic activity below 4.0 gm. per 100cc. of duodenal drainage is the best indication of pancreatic insufficiency. Amyloptic activity is very variable during the early months of life,

hence it is of little value. The volume of duodenal secretion is increased normally and in celiac syndrome as a result of secretin injection or of acid instillation into the duodenum. Pancreatic fibrosis is indicated when there is no response to the injection of secretin.—Wm. J. Snape.

PANCREAS

WALKER, H. AND BOGER, W. P.: *Adenoma of islets of Langerhans with hypoglycemia.* (*Arch. Int. Med.*, v. 75, p. 109, Feb., 1945).

Recurrent bouts of hypoglycemia may be produced by small adenomata of the pancreatic islet cells. As the adenomas grow larger the degree of hypoglycemia becomes more severe. At first the hypoglycemia may be controlled by a large intake of carbohydrate but later only surgical intervention will prove effective. Symptoms are similar to "insulin shock". A positive Babinski which disappears when the hypoglycemia is controlled is worth noting. Hunger may be present, and convulsions are common. No correlation between blood sugar level and type of symptoms has been found. Since hypoglycemia of long duration will affect adversely the central nervous system, surgical removal of the adenoma at an early date is advisable. The authors report two cases, bringing the number of patients cured by operation to a total of 56.—G. Klenner.

CATTELL, R. B.: *Pancreatoduodenal resection: report 18 cases.* (*New England J. Med.*, v. 232, p. 521, May, 1945).

In 18 patients who had been subjected to resection of the pancreas and adjacent duodenum there were three deaths. Most of the operations were performed in two stages. The necessity for the two-stage technic is dictated by the advanced age and poor condition of the patients. Most patients showed obstructive jaundice of varying degrees of severity.

Direct anastomosis of the pancreatic duct to the jejunum is made to establish pancreatic drainage of the external pancreatic secretions. This permits proper digestive processes to continue and prevents formation of pancreatic fistulas which may become serious complications to recovery. In 13 of the 18 cases followed for a period extending to two years the surgery was considered to have proven satisfactory.—Wm. J. Snape.

MCCALL, M. L. AND REINHOLD, J. G.: *An evaluation of the clinical significance of serum amylase and lipase determinations.* (*Surg. Gynecol. Obstet.*, v. 80, p. 435, April, 1945).

Patients with diseases of the pancreas, liver, or gall bladder were tested with respect to the levels of serum lipase and amylase. The Cherry and Crandall procedure was used to determine serum amylase. Serum lipase above the normal value of 1.5 was found in 12 of 13 cases of acute pancreatitis while serum amylase values above 200 mg. per cent were found in 8 out of 9 cases. In carcinoma of the head of the pancreas serum lipase was elevated more often (9 out of 16

cases) than serum amylase (1 out of 7 cases). Low serum values are of dubious importance in interpreting liver damage but low serum amylase in such conditions may have some significance. High serum amylase and lipase were found in cases with choledocholithiasis but these were associated with the presence of pancreatitis as seen at operation.—G. Klemmer.

LIVER AND GALL BLADDER

ROBERTSON, H. E.: *Preponderance of gallstones in women.* (*Surg. Gynecol. Obstet.*, v. 80, p. 70, January, 1945).

The numerous theories to explain the higher frequency of the occurrence of gallstones in women are presented. No one theory has received universal support and no single course has been proved to be the etiologic one. Most workers believe in predisposing influences and have stressed its importance in their accounts. Robertson points out that in both sexes the stones occur in greatest frequency at the age when the individual is most active sexually. Cholelithiasis has not been proved to be due to stasis in the flow of bile, bacterial infections, or any specific disease. The signs and symptoms do not appear to have any relation to the processes of formation of the stones since symptoms often occur many years following the presence of the stones. Furthermore, many gallstones are "silent".

Little evidence exists that mucin or nucleoalbumin in the bile is a factor towards precipitation of bile salts. The ratio of bile salts to cholesterol, pigments and calcium salts must be kept rigidly or precipitation occurs readily. The precipitated elements act as a nucleus for further carrying down and binding the bile material. There must also be present disturbed absorptive functions of the gall bladder to permit the stones to form.—A. Wocker.

WOHLWILL, FREIDRICH: *Diffuse infiltrative interstitial hepatitis.* (*Schweiz. Zeitschr. Allg. Path. Bakt.*, v. 2, p. 240, 1939.)

Description of two cases of acute hepatitis. Histological examination of both cases revealed marked cellular infiltration in contrast to "serous hepatitis" so much discussed recently. The first case with acute clinical course, pronounced hepatic insufficiency and jaundice succumbed after 1 week of illness. The other patient showed a subacute course without jaundice. The histological picture of this case resembled Hanot's cirrhosis. Both cases were characterized by intense inter- and intralobular cell infiltration and changes of the reticulum. In the acute case, the reticulum was destroyed. In the subacute case, regeneration of the reticulum fibrils could be demonstrated. In both cases, there was pronounced disarrangement of the architectonic structure of the liver; in the acute case, this was accompanied by necrosis of the liver cells. The author believes that cases of hepatitis are due to a toxic agent.—Courtesy Biological Abstract.

THERAPEUTICS

WATT, J.: *Acute diarrheal disorders.* (*New Orleans Med. Surg. J.*, v. 97, p. 438, 1945).

Either the Shigella or the Salmonella bacteria are responsible for most of the acute diarrheal disorders coming to the physician's attention. Differentiation between the conditions caused by the two organisms is difficult but should be made because sulfonamides are effective in shigellosis but not in salmonellosis. Differentiation by rectal swab culture is recommended. Since shigellosis is more common, the patient should be given sulfadiazine on admission, but only after a rectal swab has been made. Four grams daily should be used until the organism is identified but this treatment should be dropped if either Salmonella or negative findings are reported. If no bacteriologic study of the stools can be made, then it should be remembered that since the majority of Shigella and Salmonella infections are self limiting the illness if it is prolonged is probably due to some other organism.—W. D. Beamer.

MACKENZIE, D. H.: *Sulphasuxadine in operations on the rectum and colon.* (*Brit. Med. J.*, v. 2, p. 722, Dec. 2, 1944).

The growth of gram negative organisms as influenced by sulfonamides was studied in 30 cases of surgery of the rectum and colon. As determined by stool cultures, succinylsulfathiazole in daily 20 gram doses resulted in universal decrease in gram-negative organisms. Sulfathiazole was less effective. None of the sulfonamides used showed toxic reactions. It was concluded that a daily dose of 20 grams of succinylsulfathiazole for four days preceding operation reduces effectively the gram-negative organisms in the intestine.—F. E. St. George.

STEIGMANN, F. AND PAPPER, H.: *The medical management of jaundice.* (*Illinois Med. J.*, v. 86, p. 164, 1944).

Except in hemolytic jaundice, the pathologic changes in the liver cells of all other types of jaundice (including catarrhal, surgical infections, and toxic jaundice and the jaundice of cirrhosis, Weil's disease, and toxemia of pregnancy) are fairly identical. The differences in these diseases appear to be a matter of degree of involvement rather than type of change.

High contents of liver glycogen are beneficial in withstanding toxic changes while fatty livers are not desirable. Fat in the diet should therefore be limited. Since high blood sugar levels must be attained before glycogen becomes deposited in the liver it is necessary that the carbohydrate intake be high. If necessary parenteral dextrose therapy is used.

High protein diets should be used since low blood protein levels tend to reduce wound healing and to favor edema. However, meat is not the best protein to be used: amino acids are preferable and if necessary may be given parenterally.

Mineral intake is within normal range since mineral metabolism appears not to be disturbed. Fluids should be limited to control edema but restriction should not

be carried to the point of dehydration. Vitamins should be supplied abundantly. Choline has lipotropic action and its inclusion in the diet helps reduce liver fat. Bile salts are employed when cholerisis is desirable but of course are not used in obstructive jaundice. Since barbiturates are detoxified in the liver their use in liver damage should be avoided. Morphine and the sulfonamides are best not used because of their effect on the liver.—I. M. Theone.

CROSS, R. M.: *Penicillin in Weil's disease.* (*Lancet*, v. 1, p. 211, Feb. 17, 1945).

A 35 year old aviator developed Weil's disease. Hemolytic streptococci were cultured from the throat on the third day. The patient's condition rapidly became critical. On the fifth day slight jaundice developed and purpuric spots appeared on the chest. The jaundice became deeper and the patient began vomiting bile-colored fluid. Bile was found in the cerebrospinal fluid. Blood urea was 320 mg per cent. Leptospira were found in the urine on the 14th day. Intramuscular drip therapy with penicillin was started. After 24 hours, when 120,000 units had been given the urine was negative for Leptospira. A total of 800,000 units was given over a period of seven days. Recovery was uneventful though the patient had a hypochromic microcytic anemia.

Two guinea pigs were inoculated with the Leptospira organism. One animal also received penicillin and recovered, while the untreated control animal died.—F. E. St. George.

EXPERIMENTAL MEDICINE SECRETION

FRIEDMAN, M. H. F. AND PINCUS, I. J.: *The influence of the consistency of food on the gastric secretion.* (*Exper. Med. Surg.*, v. 3, p. 100, May, 1945).

The influence of changes in the physical state of food, rather than changes in chemistry produced by cooking, on the gastric secretion was studied in dogs with Pavlov pouches. When meat was fed in large pieces the total volume of acid gastric juice secreted during the ensuing four hours was 22 to 34 per cent more than when the same amount of meat was fed in ground form. The increase did not occur during the chemical phase, commencing only during the second hour and continuing for the third and fourth hours. The authors believe that the increased secretion is due to delayed gastric emptying of the diced-meat meal. The longer retention of the meat pieces in the stomach resulted in a longer period of contact of the meat with the pyloric mucosa and hence in a greater and more prolonged chemical phase of gastric secretion. The need in experimental studies for standardizing the consistency of a meal, in addition to its volume and composition, are pointed out.—I. H. Dougherty.

MOTILITY

LEHMANN, G.: *Gastric cardiospasm in the dog.* (*Amer. J. Physiol.*, v. 143, p. 163, Feb., 1945).

The study was carried out on 53 dogs under barbi-

turate anaesthesia. Stimulation of the central end of the cut vagus resulted in relaxation of the cardia: this was soon followed by contraction. The fibres producing the contraction were in the main vagus trunk and were cholinergic. The inhibitory mechanism was within the wall of the lower esophagus. Bilateral vagotomy interfered with the inhibitory mechanism. Cardiospasm in vagotomized animals resulted because of the predominance of the sympathetic nerves which have motor effects on the cardia. The cardia was relaxed by paralyzing sympathetic fibres with ergotamine.—M. H. F. Friedman.

ABSORPTION

MACLACHLAN, P. L. AND THACKER, C. W.: *The effect of anoxia on fat absorption in rats.* (*Amer. J. Physiol.*, v. 143, p. 391, March, 1945).

Direct measurement of fat absorption was made by determining the amount of fat remaining in the alimentary canal at certain intervals after the feedings of the fat. The rats were given standard amounts of corn oil by stomach tube and placed in chambers under a partial pressure of oxygen. Controls were similarly fed but kept at atmospheric pressure. All animals were fasted for 48 hours preceding the experiment.

Partial pressures of oxygen of 117 and 80 mm Hg (corresponding to about 8,000 and 18,000 feet altitude) were without significant influence. Partial pressures of oxygen of 63 and 53 mm Hg (24,000 and 28,000 feet altitude) resulted in definite decrease in the amount of fat absorption. The threshold for fat absorption appears to lie at a partial pressure of oxygen between 80 and 63 mm Hg.

This study indicates that the degree of anoxia must be much more severe than that which is still compatible with life to interfere with fat absorption.—M. H. F. Friedman.

PATHOLOGY

STETTEN, DE W. JR., AND SALCEDO, J. JR.: *The effect of chain length of dietary fatty acid upon the fatty liver of choline deficiency.* (*J. Nutrit.*, v. 29, p. 167, March 1945).

Rats kept on choline deficient diets were fed even-numbered fatty acids as the ethyl esters. The homologous series tested ranged from butyric acid to stearic acid and each was fed at a 35 per cent level of the diet. The livers were analyzed for fat after the animals were kept for two weeks on their respective diets. It was found that as the chain length of the fatty acid fed was decreased there was an increase in the degree of fatty liver. Fatty acids of less than 12 carbon atoms had no effect on the liver fat. It was observed incidental to the main investigation that all animals fed ethyl laurate developed a fatal myocarditis.—M. H. F. Friedman.

FIELD, J. B., GRAF, L., SVEINBJORNSSON, A., AND LINK, K. P.: *Effect of methylxanthines on the hypocoagulability produced by chloroform liver damage in dogs.* (*Fed. Proceed.*, v. 4, #1, p. 89, March 1945).

Chloroform is known to have a hepatotoxic action resulting in hypocoagulability of the blood due to

prothrombin and fibrinogen deficiency. Chloroform was administered to dogs by stomach tube. This technique gave a reproducible reduction in prothrombin and fibrinogen levels. Methylxanthines (caffeine, theobromine, and theophylline) have been shown to induce elevated levels of plasma prothrombin and fibrinogen resulting in antagonizing the effect of the chloroform. A partial protection was afforded by creatine, creatinine, guanidine, and uracil.

Following a test administration of chloroform, icterus was frequently observed in plasma, and the capacity of the liver to remove the bromsulphalein test dye from the blood stream was considerably reduced. These indications of hepatic dysfunction were not prevented by supplementary feeding of methylxanthines even when they prevented a depression in plasma level of fibrinogen or a hypoprothrombinemia.—I. H. Dougherty.

ANNEGERS, J. H., DRILL, V. A., HABEGGER, J., IVY, A. C., AND ATKINSON, J. A.: *Hepatotoxic action of arsenicals*. (*Arch. Dermatol. Syph.*, v. 51, p. 112, 1945).

Dogs with permanent biliary and duodenal fistulae were used to determine (a) the effects on cholic acid synthesis of intravenous injections of neoarsphenamine and mapharsen, and (b) the value of dehydrocholic acid in preventing the hepatotoxic action of these arsenicals. A dose of 300 mg. of neoarsphenamine did not consistently depress the cholic acid output. Mapharsen in 60 mg. doses depressed the cholic acid output on an average of 34%. The administration of dehydrocholic acid orally before and after the injection of mapharsen raised the cholic acid depression to an 18% average, but the results were not statistically significant. —Courtesy Biological Abstract.

PATHOLOGICAL CHEMISTRY

WADE, L. J. AND RICHMAN, E. E.: *The cephalin-cholesterol flocculation test*. (*J. Lab. Clin. Med.*, v. 30, p. 383, Apr., 1945).

Cephalin-cholesterol tests were run on 1500 samples of human serum, 500 of which were from patients whose conditions had been diagnosed beyond doubt. In normal healthy controls there was no flocculation, but in the presence of infection, allergic disease and during the puerperium or neonatal period false positives occurred. The test is believed to have both prognostic and diagnostic value in cases of acute hepatitis, catarrhal jaundice and cirrhosis, or in the presence of other diffuse parenchymatous liver disease.—R. L. Burdick.

LARSON, E. A. AND EVANS, G. T.: *Biliverdin icterus*. (*J. Lab. Clin. Med.*, v. 30, p. 384, April, 1945).

The test for serum biliverdin is done on an Evelyn colorimeter and the principle of the test is the increasing light absorption of biliverdin in passing from green to red wave lengths. In normal sera the biliverdin concentration is low and is not detectable. Biliverdin values are present in direct proportion to bilirubin values. In a series of tests on 14 patients it was noted

that biliverdin values can change markedly regardless of the change of the total jaundice. During a period of high caloric intake, biliverdin disappeared although the jaundice remained unchanged. Biliverdinemia was not noted in hemolytic jaundice, therefore its presence is believed to give evidence of regurgitation.—R. L. Burdick.

METABOLISM AND NUTRITION

BESSY, OTTO A.: *Tissue responses to vitamin deficiencies*. (*Growth, Suppl.* to v. 6, p. 95, 1942).

A great variety of tissue changes result from the numerous vitamin deficiencies. Some of these are specific; others such as those due to inanition are common to several of the deficiencies. The morphological responses to vitamin A, ascorbic acid, and thiamine deficiencies are discussed and it is pointed out that experimental nutrition as a research tool in studies of growth and development has potentialities far beyond its present use.—Courtesy Biological Abstract.

LORENZ, A. J.: *Army hospital diets—past and present*. (*J. Am. Dietetic Assoc.*, v. 20, p. 430, 1944).

Parched grain was the traditional "K" ration of armies from the time of Xerxes through the Civil War. Army hospitals are necessarily a part of war. The first authentic food list for an army hospital (London, circa 1550) mentions "pork, mutton, ribs of beef, salted and pickled herring, bread, rye flour, and beer." The oldest known menu (London, 1686) gave a person's daily allowance as bread, 10 oz.; and butter, 2 oz.; porridge (soup) 16 oz.; cheese, 4 oz.; and beer, 3 pts. Interesting old records show the gradual advance until Civil War times when breakfast was coffee with milk, cold meat and bread, which contrasts greatly with an overseas breakfast of today: grapefruit, oatmeal, milk, pork sausage, hot cakes, bread, butter, syrup, and coffee.—Courtesy Biological Abstract.

MISCELLANEOUS

MORRISON, L. M. AND SPIEGEL, E. A.: *Demonstration of visceral pain by determination of skin potentials*. (*Arch. Intern. Med.*, v. 22, p. 827, June 1945).

This reports a study to develop a method for the localization of pain objectively. The pain studied was that which was associated with diseases of internal organs. The pain detector used was based on the principle of determining changes in electric potentials of the skin. Pain of psychogenic origin or healed organic disease usually gave no increases of skin potentials or else increases which did not exceed 9 millivolts. On the other hand increase of skin potentials by 10 millivolts or more was shown by cases with active organic disease. The potential was measured in the skin area overlying the affected organ. Lack of skin potential did not exclude organic disease. The authors conclude that visceral organic disease may well be demonstrated by high skin potentials and that latent pathological changes may be found by this means.—I. H. Dougherty.

The Clinical Significance of Cholesterol

by

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IN contradistinction to the nitrogenous products, the normal cholesterol content of the blood serum or plasma in groups of individuals fluctuates within wide limits. Although much work has been done on the cholesterol level of the blood in disease, this factor has not always been fully recognized. Results have also been confusing for two other reasons. Many reports include only a small number of patients, whereas for conclusions of any value large numbers of patients must be studied in various stages of the disease under consideration. Then, too, clinical symptoms are not often correlated with laboratory data as they should be.

In order to arrive at significant conclusions, normal cholesterol values must be defined for both male and female in various age groups. Weinhouse (180) has recently reviewed the methods of determining cholesterol, its metabolism, and its physiological variation.

The range of blood cholesterol varies with the method used. Therefore, the standard of normal must be determined in each laboratory. With the customary colorimetric method, the average has been found to be approximately 150 to 180 mg. per 100 cc. of serum or plasma, with a deviation of about 40 mg. (180) and a maximum of 230 mg. (32). Cholesterol levels determined on whole blood are lower, because red blood cells contain only small amounts of free cholesterol and the cholesterol esters are present in minute quantities, if at all. The variation of values in apparently normal individuals has been extended in more recent studies. In a group of 66 normal men observed by Page, Kirk, and associates (124), it was found that the plasma cholesterol ranged from 109 to 376 mg. per cent, with a mean of 232 and a standard deviation of 62 mg. Sperry (161), working with 91 persons of both sexes, found values ranging from 131 to 392 mg. per cent, with an average of 209. The higher range is probably due to refinement of technique and better extraction and separation of the cholesterol from the blood.

Blood cholesterol is found mostly in the form of an ester or in combination with fatty acids. Most observers (32, 111, 117, 156, 160, 161) have reported the relation of free to total cholesterol to be a constant value of approximately 25 to 40 per cent. Sperry (161), taking samples postmortem from humans who had died suddenly, and from healthy and diseased children, found that the minimum amount of free in total cholesterol was 24.3 per cent, the maximum 30.1 per cent, and the average 26.9 per cent, with a standard deviation of 1.4 per cent. In his opinion, the percentage of free in total cholesterol is a physiological constant which may be of considerable value in the study of cholesterol metabolism in disease. Contrary

to this, Page and associates (124) reported values ranging from 22 to 72 per cent in normal men, a discrepancy which requires further elucidation.

One point to be settled is whether the wide normal range of cholesterol concentration depends upon fluctuations in one individual over a period of time or variations between persons. Sperry (162) found remarkably constant cholesterol levels in each of 25 adults whom he studied for periods up to 28 months. Muller and Talbott (113), in studying four healthy men for three or four weeks, found individual plasma cholesterol variations of 3 to 33 mg. per cent. A study of three of these men one year later showed a somewhat higher variation (minimum 13, maximum 55 mg. per cent). On the other hand, the serum cholesterol of these men varied considerably from each other. Man and Gildea (98) examined the serum lipids in four males and six females at varying intervals for three months to four years, and found that the minimum and maximum cholesterol varied by as much as 31 per cent. These differences were not related to changes in the hemoconcentration when serum proteins were employed as a criterion of blood volume. Neither were they related to slight changes in body weight, menstrual cycle in the female, time of year, or intake of food. Similar observations were made by Schube (151) in a study of 10 individuals over a period of four months. Total cholesterol varied from 100 to 198 mg. per cent, with a change from week to week of 0 to 73 mg. When the blood cholesterol was considered in relation to the individual mean over a long period it fluctuated over a range of 19 to 47 mg. Wilkins, Fleischmann and Block (188) observed fluctuations up to 83 mg. per cent in normal children but found no significant connection with the time of feeding. In a number of normal children whose serum cholesterol was determined during the day, the fluctuations were never greater than 33 mg. per hundred cubic centimeters of blood. Boyd (21) found that normal adults ingesting three ordinary meals a day showed only slight variations of the plasma cholesterol and other lipids throughout the day.

In the light of these investigations it may be seen that the serum cholesterol of an individual remains remarkably constant throughout the day, and that neither the total cholesterol content of blood plasma or serum, nor the proportion between the various cholesterol fractions is altered significantly after meals of high cholesterol content (52, 161, 173) or after the ingestion of cholesterol in oil (9).

From reviews of literature on the influence of the diet on the cholesterol level made by the author in 1930 (112) and more recently by Weinhouse (180), it may be concluded that alimentary hypercholesterolemia after ordinary meals or after meals containing considerable cholesterol has not been definitely proved.

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If changes are observed, the increase is small. In this connection it is interesting to note Blotner's (15) attempt to apply as a diagnostic criterion in various diseases the changes in the cholesterol content of the blood which occur after the ingestion of fat. The method is based on the principle of the sugar tolerance test except that, instead of dextrose, 500 cc. of 20 per cent cream (equivalent to about 100 gm. of fat) are ingested. He found that normal persons show no significant change; in thin persons the cholesterol remained constant or decreased slightly; in obese individuals the cholesterol increased for a period of six hours, then gradually declined. Unfortunately, Rony and Levy (141), under the same conditions, did not find any change in the plasma cholesterol level in 18 markedly obese individuals. This has been recently verified by Oppenheim and Bruger (121). Ingestion of dextrose and large amounts of water do not influence the cholesterol level significantly.

Ingestion of large amounts of cholesterol in oil may cause a temporary lipemia and an increase in cholesterol. It may be concluded that under normal dietary conditions the fluctuations in the concentration of cholesterol are of slight or no clinical significance.

Even though as a rule an alimentary hypercholesterolemia does not occur, the possibility exists that over long periods diets, either high or low in cholesterol, may influence the level of this substance in the blood. Luden (95), in experiments on herself, demonstrated that a diet high in eggs, butter, and meat over an extended period did increase the cholesterol level, while a vegetable diet decreased the cholesterol concentration in the blood. This was verified by Gardner and Gainsborough (52). Similar conclusions were arrived at by Okey and Stewart (120), who for a period of a month studied four healthy women placed on 1) a low-cholesterol diet; 2) a diet containing moderate amounts of cholesterol in the form of egg yolks and liver; and 3) a diet low in food cholesterol to which an amount of cholesterol equivalent to that in the second diet had been added. They found that the mean values for the month were slightly higher on the diet containing 3.1 gm. of cholesterol daily from natural foodstuffs than the diet containing the equivalent amount of added cholesterol. Their mean values were: Diet I, 154; II, 167; III, 159.3 mg. per hundred cubic centimeters of blood. These observations could not be confirmed by Turner and Steiner (173) who studied nine patients for periods of 12 to 14 months, and they concluded that no relation exists between the blood cholesterol level and the type of diet. On the other hand, Steiner and Domansky (164) observed a rise in total blood cholesterol from 40 to 218 mg. per cent when they fed 10 individuals daily for six to ten weeks 100 gm. of egg yolk powder containing 8 gm. of cholesterol and 14 gm. of lecithin. They ascribed the rise to the presence of lecithin. It is evident, therefore, that ingested cholesterol alone or mixed with fat has very little influence on the level but that when lecithin is added an appreciable increase is produced in the cholesterol concentration, probably be-

cause of the more efficient absorption of the cholesterol.

The effect of starvation has been studied experimentally, with variable and contradictory results (112, 180). A few reports on man are available (5, 15+) which indicate that starvation for short periods up to six days produces a hypercholesterolemia which decreases rapidly after feeding, regardless of the food taken. It has been suggested that this hypercholesterolemia is due to destruction of tissues and increased metabolism of fat. On the other hand, undernourishment may cause a decrease in the cholesterol concentration in the blood. Man and Gildea (97) report a study of 10 variously malnourished patients in whom the cholesterol content varied directly with the state of nutrition. When the nutritional state improved the cholesterol rose from 32 to 101 mg. per cent within two to ten weeks. White and Hunt (186) found blood cholesterol values to be distinctly higher in overnourished than in normal children. On the other hand, Wilkins, Fleischmann, and Block (188), working with 13 children from 30 to 130 per cent overweight, found serum cholesterol values ranging from 115 to 253 mg. per cent, with an average of 164 mg. per cent, values which are slightly lower than that of normal children. Bruch (30), studying 89 obese children, also found cholesterol values within the normal range, with a mean of 200 mg. per cent and a standard deviation of ± 38 .

There is no doubt that the cholesterol concentration in an individual fluctuates, but the mechanism is not understood. Meager data reviewed by Weinhouse (180) suggests that changes may occur in the cholesterol level because of muscular work and emotional states at the time when the blood is taken. The fluctuations in individuals, however, are small in comparison with the variation between individuals in a group (53). Some of the differences may be explained, perhaps, by the state of nutrition and long-continued dietary habits. Some possible light has been thrown on the subject by the study of the relation of the cholesterol concentration in the blood to body build and age.

Gildea, Kahn, and Man (58) studied men and women of different types of body build, free from any endocrine disturbances. The stocky, heavy male, or pyknic type, showed a blood cholesterol concentration averaging 230 mg. per cent, while the slender, asthenic type (leptosomic) averaged only 168 mg. per cent, and the intermediate group 203. In the women these differences were not so clearcut, possibly because of the difficulty in distinguishing between the asthenic and pyknic types. The average cholesterol values were respectively 196 and 205 mg. per cent. Similar conclusions were drawn by Mjassnikow in 1927 (109) from a study of asthenic and hypersthenic individuals.

Studies have been made on the differences in cholesterol value according to age. Serum cholesterol from newborn infants, determined on blood obtained from the umbilical cord by Muhlbock and Kaufmann (111) averaged 70 mg. per cent, a distinctly low value. During the first three or four days of life there was a marked increase, the average rise from the first to

the fourth day being 91 to 137 mg. per cent. After this, the value remained constant. Sperry (160) found a range of 71 to 192 mg., with an average of 133 mg. ± 25 , in infants 4 to 25 days of age. (This range was equivalent to 168 per cent of the minimum value.) In a series of determinations in adults, the range was from 130 to 350 mg., with an average of 209 and a standard deviation of ± 50 mg. (This range was equivalent to 169 per cent of the minimum value.) The ratio of combined to free cholesterol in infants differed from that in adults by being lower and by having a wider range. In infants the percentage of combined cholesterol ranged from 41 to 72 per cent, and in adults from 70 to 75 per cent. The mechanism controlling the proportion of combined and free cholesterol is not yet fully established in the neonatal period. In infants over 14 days old, the ratio approached the normal adult level. Sperry did not observe any definite influence by physiological factors on either ratio or total cholesterol.

During childhood the cholesterol increases gradually to normal adult values in both sexes. Hurxthal and Simpson (79) claim that there is a gradual increase as age advances. Muhlböck and Kaufmann (111) also observed an increase with age in both the free and combined blood cholesterol of women. Their averages were 200 mg. between 20 and 30 years of age; 217 between 30 and 40; 213 between 40 and 50; and 261 mg. between 50 and 60 years of age. On the other hand, Page, Kirk, and associates (124) could not demonstrate any effect on the plasma cholesterol and its esters in a group of adult men from 21 to 91 years of age.

Two physiological conditions in women, namely menstruation and pregnancy, cause changes in the cholesterol concentration of the blood. Okey and Boyden (119), in a study of 16 normal young women, showed that there is a slight premenstrual rise, followed by a distinct fall at the onset and during menstruation, then a sudden rise during or shortly after the cessation of bleeding, followed by a decline to normal values. These findings have been verified by Muhlböck and Kaufmann (111). The fall of blood cholesterol during menstruation is caused by a decrease in the combined cholesterol (111, 117). Man and Gildea (98), however, claim that the individual variations of the cholesterol level in women cannot be related to the menstrual cycle and that, moreover, the changes observed in the cholesterol level of males exceed those of females.

That an increase of cholesterol, as well as other lipids, occurs during pregnancy, is a well-established fact. The reader is referred to the review by Boyd (20), who summarized the findings in the literature. There is a general agreement that the cholesterol begins to change early in the second trimester. There is a gradual rise up to the eighth month; then the cholesterol remains stationary but high through the puerperium. The average increase is about 25 per cent of normal. Fürger (32) claims that between the eighth month and parturition the cholesterol falls rapidly. During the puerperium it again increases, and may

reach values higher than that at eight months. Boyd (22) found that when normal lactation was prevented by drying up the breasts, the decrease of plasma lipid levels was inhibited, stopped, or even reversed. Changes in the lipemia of pregnancy involve only the plasma, and the proportion of free cholesterol to cholesterol esters remains within normal limits, thus placing the cholesterolemia and lipemia of pregnancy in the same class as those seen in diabetes, nephritis, chronic alcoholism, and hemorrhagic anemia. Slemmons and Stander (155), reviewing the literature and presenting their own cases, conclude that there is no significant variation in the cholesterol from that of normal gravid women during toxemias of pregnancy and eclampsia.

* * *

BLOOD CHOLESTEROL IN DISEASE

The relation of cholesterol to thyroid disease and basal metabolism

That the thyroid gland has an influence on the basal metabolic rate is a well-established fact. A definite relationship between the basal metabolism and the blood cholesterol in thyroid disease was established by Epstein and Lande (47) in 1922. In 9 out of 14 patients with long-standing thyrotoxicosis they found that the lowest metabolic rate corresponded to the highest level of cholesterol and vice versa. One patient with thyrotoxicosis showed a gradual increase from 146 to 218 mg. per cent over a period of seven months. This was satisfactorily explained, in their opinion, by a complicating nephritis. Whether the basal metabolism remained high during the rise in cholesterol is not stated.

In 10 cases of toxic thyroid adenoma with toxic symptoms and increase in the basal metabolic rate the inverse relationship held true in only 6 cases. In the other four patients (females) the cholesterol was normal or slightly diminished in spite of increased metabolic rates. The fact that three of these women were at the climacteric and the fourth was 61 years old, might explain the lack of relationship between the cholesterol level and the basal metabolic rate. In a case with definite thyroid adenoma in which the toxic symptoms developed while the patient was under observation, the basal metabolic rate gradually rose from +9 to +24 and the cholesterol fell from 328 to 238 mg. per 100 cc. of blood. Ten days after thyroidectomy the basal metabolic rate had fallen to normal and the cholesterol had risen to 276 mg. per cent.

In 11 cases of suspected hyperthyroidism Epstein and Lande found that the basal metabolic rate varied between -10 and +15 per cent. Blood cholesterol was normal in six, increased in four, and below normal in one individual with gastric neurosis who vomited all food immediately after eating. In nontoxic thyroid enlargements the basal metabolism and cholesterol concentrations were normal. On the other hand, the blood cholesterol was markedly elevated in patients with low basal metabolic rates and clinical signs of myxedema.

From the above study Epstein and Lande concluded that in thyroid disease an inverse relationship exists between the basal metabolic rate and the cho-

lesterol level of the blood, but that this relationship is not invariable. This they explained by the well-known fact that in some cases of thyroid disease the basal metabolism does not correspond to the severity of the condition as observed clinically, because the damage outlasts the elevation of the basal metabolic rate.

Subsequent work has been devoted to proving or disproving that the blood cholesterol level actually fluctuates with the activity of the thyroid gland and that an inverse relationship exists between the blood cholesterol and the basal metabolic rate in untreated patients as well as in those who have had various forms of therapy. It is evident that if a variation in blood cholesterol is associated with the variation in thyroid activity, blood cholesterol can be used as an index of the functional state of this gland and as a corroborative test of the basal metabolic rate.

Studies on large series of patients support the opinion that low blood cholesterol values are associated with hyperthyroidism (23, 74, 88, 99, 103, 116, 125, 148, 179). This decrease in cholesterol concentration does not depend on the undernutrition common in this disease (74, 99) nor on the hemoconcentration (99). Some authors (23, 74, 183), in addition, confirm the inverse relationship between the level of blood cholesterol and the basal metabolic rate in thyrotoxicosis, while others (99, 103) claim that such a relationship does not exist.

In 47 patients with proved hyperthyroidism, Mason, Hunt, and Hurxthal (103) found cholesterol values ranging from 71 to 183 mg. The average basal metabolic rate was +57 per cent. They concluded that although cholesterol values were low in thyrotoxicosis there was no definite correlation between the height of the metabolism and the cholesterol value in this disease.

In subsequent studies on 283 patients with exophthalmic goitre Hurxthal (74) found cholesterol values ranging from 53 to 245 mg. per cent, with an average of 127, in those who had received no iodine. The lowest average values were found in patients in or near thyroid crisis. The next lowest average value was associated with auricular fibrillation in toxic goitre. Sixty-three patients with toxic adenomatous goitre showed cholesterol values which, although low, were higher than those of exophthalmic goitre patients. In a series of 146 cases of nontoxic goitre the cholesterol fell within a normal range, although widely scattered. Hurxthal found that chronic thyroiditis was associated with values higher than those of any other thyroid disease except myxedema, excluding the element of infection and mild hyperthyroidism often seen in the early stages. He concluded that there was a reciprocal relationship between the average values of cholesterol levels and basal metabolic rates. On the other hand, Man, Gildea, and Peters (99), in a series of carefully selected patients with uncomplicated hyperthyroid disease, could not demonstrate that these two values were inversely proportional, because of the variability of the cholesterol levels.

Boyd and Connell (24) drew the conclusion that five out of six patients with hyperthyroidism may be expected to have plasma cholesterol values below

those of normal individuals, even though the variation from individual to individual is large.

Several authors, however, have contradicted the above findings. At the Mayo Clinic Luden (96) found normal values in 35 patients with exophthalmic goitre and high basal rates. Normal values have been reported by others (10, 88, 179). Gardner and Gainsborough (54), working with 12 cases, found values lower than the average normal, but nevertheless within the normal range. Still others have reported increased cholesterol levels in toxic cases (93, 104, 177). The discrepancy may be accounted for by several factors, as has been pointed out by Man, Gildea, and Peters (99). There may be inaccuracies and differences in methods; and differences in choice of cases, care not being taken to eliminate symptoms of extrathyroid origin due to disorders of the vegetative nervous system. The presence of elevated serum cholesterol in these conditions has been shown by Gildea, Man, and Biach (60). Constitutional factors may also play a role. It has been demonstrated (58) that pyknic individuals, who normally have values in the upper normal range, may have a real reduction in the cholesterol level even though the value does not fall below normal. Studying an inadequate number of patients explains some discrepancies, since small series may be weighted in any direction.

There is general agreement (10, 47, 75, 88, 99, 116) that with few exceptions preoperative treatment with iodine in hyperthyroidism causes an increase in the average cholesterol level and a decrease in the basal metabolic rate. This is also true after subtotal thyroidectomy. Hurxthal (75) noted an increase, often above normal, in cholesterol six days after operation. Several months after thyroidectomy there is a fall in the cholesterol level without a corresponding rise in the basal metabolic rate. Man, Gildea, and Peters (99) found that all but 6 of 31 hyperthyroid patients showed a drop of 7 to 65 per cent in basal metabolic rate and an increase of 10 to 100 mg. per cent in cholesterol after the administration of Lugol's solution. Of the six patients who did not respond to Lugol's solution, three showed an increase in cholesterol levels, but showed a negligible change in basal metabolic rates. The other three patients had initial cholesterol values of 141 to 197 mg. per cent, and did not show any change. They all exhibited symptoms of vasomotor instability, myasthenia, depression, and anxiety of a marked degree, conditions associated with a lability of serum lipids (60) and often values lower than normal (27), which may account for the lack of response to Lugol's solution. These patients improved only slightly after thyroidectomy. In every case after thyroidectomy the cholesterol increased and the basic metabolic rate fell. In 30 patients the average cholesterol concentration before medication with Lugol's solution was 139 mg. per cent, and 1 to 8 weeks after the operation, 235. In some it rose sharply, then fell to a constant level four or more months after operation. The height of the rise, however, was not related to the degree of improvement. They concluded as Hurxthal (75) had previously that there is a defi-

nite correlation between the level of serum cholesterol and the activity of the circulating thyroid hormone, and that in those cases of hyperthyroidism with normal values before treatment it is reasonable to assume that the thyroid secretion had either reduced the cholesterol from levels above normal or that its effect was counteracted by factors which tended to elevate the lipoids.

If the level of serum cholesterol is an indication of thyroid activity, it can be used as an index of the gravity of the disease, and is of value in determining the surgical risk and prognosis of the individual case. This was pointed out by Epstein and Lande (47) and Larroche (88) and confirmed by Mason, Hunt, and Hurxthal (103). They observed that patients with low cholesterol values were severely toxic clinically and were poor surgical risks. Hurxthal states that if the cholesterol is below 100 in toxic goitre without acute infection, the patient is probably very toxic. If the cholesterol is above 180, with or without previous administration of iodine, there is moderate toxicity. If, after the administration of Lugol's solution, the patient does not improve clinically and if the basal metabolic rate shows little or no tendency to fall, and if the serum cholesterol does not rise, thyroidectomy in all probability will not be effective.

On the other hand, Man, Gildea, and Peters (99) claim that in patients with clear-cut symptoms of hyperthyroidism the problems of diagnosis and prognosis are relatively simple anyhow, and are not further clarified by the level of the blood cholesterol. They found that in complicated cases the initial level of the cholesterol is no criterion of the patient's response to thyroidectomy and that since the factors which control the levels of lipoids are not sufficiently well understood, these values should not be used to determine the advisability of thyroidectomy.

The initial level of serum cholesterol is of very little assistance in diagnosing hyperthyroidism (27, 47, 99, 104) but it supplies corroborative evidence of the more important clinical findings and the behavior of the basal metabolic rate, and may be of value when an accurate basal metabolism cannot be obtained (99). If, on the other hand, repeated examinations reveal a progressive decline of cholesterol in the absence of conditions such as Addison's disease, uremia, or food deficiency, this may be taken as a presumptive evidence of thyrotoxicosis even if the initial level is above normal (47). Likewise, in the absence of factors which tend to produce hypercholesterolemia, an increased blood cholesterol level is strong evidence against thyrotoxicosis (47, 75). Hurxthal (75) claims that if the cholesterol level is above 200 mg. per cent, the condition is not likely to be hyperthyroidism unless there has been a complete remission with iodine. He points out that there are patients with hypertension, goitre, and basal metabolic rates as high as +60 to +70 per cent, in whom the clinical evidence is against hyperthyroidism. In such cases cholesterol values of 160 mg. per cent or more are found which are out of proportion to the basal rate. In his opinion this serves as a definite indication that the thyroid is not the cause of the elevated metabolic rate.

The relationship of cholesterol concentration in

the blood to thyroid insufficiency is much more clear-cut than in hyperthyroidism. A marked increase has been found in the spontaneous myxedema of the adult (23, 47, 54, 59, 76, 103, 104) as well as in juvenile myxedema (29, 67, 188), in cretins (29, 76, 67), in the postoperative myxedema of subtotal or total thyroidectomy (16, 61, 76, 99, 183), and after roentgen therapy (76).

Mason, Hunt, and Hurxthal (103) in 23 myxedematous adults found a cholesterol range of 217 to 500 mg. per cent, with an average value of 321, a figure considerably above their normal maximum of 230. The average basal metabolic rate was —30 per cent. The serum cholesterol, however, was below 250 mg. per cent in 4 patients and below 300 in 11 of the 23 patients. It is also possible for obvious myxedema to exist with cholesterol values within the normal range (76, 79, 188). Hurxthal (76) claims that this does not nullify the statement that hypercholesterolemia is characteristic of thyroid deficiency because, considering the wide normal range, a high normal value in some individuals may represent a 100 per cent increase over their normal levels. Wilkins (188) points out that the marked instability of serum cholesterol in hypothyroidism of children may explain the low values frequently found in this condition.

In a subsequent report of 30 cases of spontaneous myxedema with cholesterol values up to 500 mg. per cent, Hurxthal (76) found 5 patients who had a basal metabolic rate between 0 and —12 per cent. Since such readings may be obtained under the most favorable conditions they may be grossly misleading. Marked clinical evidence of myxedema and hypercholesterolemia without a significant decrease in the basal metabolic rate has been observed by others (18, 103). Boothby, Berkson, and Plummer (18) found basal metabolic rates of —5 to —45 in clinically diagnosed cases of myxedema. Hurxthal (76) found that in myxedematous patients the percentage increase in cholesterol due to thyroid deficiency is four times as great as the drop in the basal metabolic rate. Therefore, the cholesterol concentration of the blood is much more specific than the basal metabolic rate as an indicator of thyroid deficiency. Consequently, hypercholesterolemia may be considered of thyroid origin if not explainable on any other basis. If a low basal rate and a high cholesterol level are both present, the correct diagnosis is most likely hypothyroidism. On the other hand, a normal cholesterol concentration renders a diagnosis of hypothyroidism unlikely, although it does occur in myxedema. Gildea, Man, and Peters (59) state that a cholesterol value below 275 mg. per cent is against a diagnosis of hypothyroidism. McGee (104), on the other hand, claims that a single cholesterol determination is of no value whatever in diagnosis.

The correlation of the clinical findings and the increased cholesterol level in myxedema is often striking. Mason, Hunt, and Hurxthal (103) concluded from their observations that just as a low cholesterol value in hyperthyroidism indicates severe thyrotoxicosis so in hypothyroidism a high cholesterol concentration indicates severe myxedema, and that in the latter

condition the blood level reflects the patient's condition more accurately than does the basal metabolic rate.

In juvenile hypothyroidism, blood cholesterol determinations are of special value (29, 188). As a rule, thyroid activity is estimated by the basal metabolic rate, but this procedure is difficult to carry out in children and the standards for calculating the rate in this age group are unsatisfactory. The deviation from standards which are derived from data on normally developed children do not apply to dwarfs and giants (146) and the low oxygen consumption of adipose tissue causes the basal metabolic rate of obese children to be subnormal if the standard is based on weight and surface area (165, 170). Talbot (165) suggested that a standard referring the basal caloric requirements to height alone has advantages.

Wilkins and associates (188) studied the relation of serum cholesterol and the basal metabolic rate of a group of children with unmistakable hypothyroidism and compared them with a group of presumably normal children, a group of dwarfs who had failed to respond to thyroid therapy, and a group of obese children. They found that the basal rates of the normal children fell within the limits of ± 10 with both the Boothby-Sandiford and Talbot height standards. Most of the hypothyroid children varied from -19 to -32 with the Boothby-Sandiford standard, but two of the group had values which were consistently within normal limits. The metabolic rates of the obese children when calculated by the Boothby-Sandiford standard, were frequently as low as those of the hypothyroid children, but when calculated by Talbot's height standard they were either within normal limits or considerably above it. Topper and Muller (170) also found that obese children have a normal or slightly increased metabolic rate. There was no evidence that a low Boothby-Sandiford basal metabolic rate is an indication of hypothyroidism in an obese child. The concentration of serum cholesterol in the group of normal children varied from 96 to 308 mg. per cent, with an average of 188. Similar values have been found by others (29, 92). In 21 untreated hypothyroid children the concentration varied from 145 to 660 mg. per cent, with an average of 308. The concentration of serum cholesterol was frequently above the normal level, but it was within the normal range in some severe cases of hypothyroidism. Slight differences were noted between the cretins and those with the juvenile form of hypothyroidism. The cretins varied from 145 to 522 mg. per cent, with an average of 276, while the other group had a range of 208 to 660 with an average of 352. Lower cholesterol values were found among cretins under two years of age than among older hypothyroid children. Age may, therefore, exert some influence, but it is not the only factor, because some young cretins had high cholesterol values and some of the older hypothyroid children had low values. These workers concluded that although a high serum cholesterol level is suggestive of hypothyroidism in the absence of other conditions, the absence of this finding does not exclude hypothyroidism.

Myxedema produced by thyroidectomy in exophthalmic goitre occurs with a fair degree of frequency, and as in the spontaneous variety it is accompanied by hypercholesterolemia (76, 99). Postoperative myxedema is more likely to occur in chronic thyroiditis than in ordinary exophthalmic goitre (74, 76). Hypercholesterolemia, variable in degree, was also reported by Gilligan, Volk, Davis, and Blumgart (16, 61), and Hurxthal (79) after total removal of the thyroid gland in the treatment of intractable chronic heart disease. There was a decrease in the basal metabolic rate and an increase in the cholesterol concentration of the blood as early as the end of the first week post-operatively. They were the earliest evidences of hypothyroidism, and in some cases the height of serum cholesterol concentration agreed with the clinical findings more exactly than the basal metabolic rate. Untoward symptoms were observed when the cholesterol concentration rose above 300 mg. per cent.

Although hypercholesterolemia is not pathognomonic of thyroid deficiency, it is an abnormality as consistent as any in this disease and consequently important from the diagnostic point of view in both adults (17, 76, 79) and children (67, 76, 188). In dwarfs and in cases with features of hypothyroidism, studies on cholesterol metabolism may fail to reveal evidences of thyroid deficiency. This is of value in excluding an erroneous diagnosis (188). There is a form, called imperceptible myxedema (76), in which the physical findings are not characteristic and the condition is unrecognized. This type, often seen after thyroidectomy and roentgen treatment, may be transient and is associated with hypercholesterolemia. However, if thyroid medication does not benefit a patient who has a basal metabolic rate of -20 or lower, but has a normal blood cholesterol and shows no clinical signs of myxedema, thyroid deficiency is probably not responsible for the low basal rate (103).

The significance of hypercholesterolemia as a diagnostic aid is further enhanced by the response to thyroid therapy. The reduction of the blood cholesterol and an increase in the basal metabolic rate to normal are striking features which were first described by Luden (96) and subsequently confirmed by others (23, 59, 76, 79, 103, 104, 173). Cholesterol determinations in addition provide a test which may be used as a measure of the efficacy of treatment in thyroid disease. The response is prompt, occurring within three to four weeks (78). If little or no response is obtained with adequate medication, the diagnosis of myxedema as a rule should not be made even in the presence of a high cholesterol concentration and a low basal metabolic rate, findings considered presumptive evidence of thyroid deficiency.

The determination of blood cholesterol and other lipids may be of value in the diagnosis of mild hypothyroidism. This is especially true in patients who present one or two symptoms such as mental or physical sluggishness, coldness and numbness of the extremities, vague pain in joints, menstrual disturbances, dry or rough skin, or brittle nails and subnormal metabolic rates, all suggestive although not positive evidence of decreased thyroid activity. Boyd and

Connell (25), studying such a group of patients, found that 19 had normal blood lipids and an average basal metabolic rate of —14 per cent. This group did not improve on thyroid medication. In a similar group of 16 cases provisionally diagnosed as mild hypothyroidism, which subsequently did improve with thyroid therapy, the average basal metabolic rate was not as low as that of the preceding group but the cholesterol and plasma lipids were increased. They felt that in these cases the basal metabolic rate was less reliable than the estimation of plasma lipids as an aid in arriving at the diagnosis of true mild hypothyroidism. Since only half the patients presenting symptoms of mild hypothyroidism were actually suffering from a deficiency of thyroid function, these workers believe the plasma lipids furnish a simple means of differentiating and diagnosing cases of mild hypothyroidism.

The reaction of the serum cholesterol to thyroid medication in children with thyroid deficiency has been studied recently by Wilkins, Fleischmann, and Block (188). They found that the daily administration of one-half-grain doses caused the serum cholesterol to decrease from 78 to 305 mg. per cent, a reduction of 35 to 57 per cent below the control level. When larger doses (2 grains) were administered daily, the decrease was from 131 to 385 mg. per cent, a reduction of 44 to 63 per cent below the original value. In the control group of children receiving 2 grains of desiccated thyroid the decrease of serum cholesterol was never greater than 77 mg. per cent, and the reduction never exceeded 30 per cent, which is within the range of spontaneous fluctuations. In many of the control children the decrease of the cholesterol was insignificant; occasionally an actual increase was observed.

There are many objections to measuring sensitivity by giving daily doses of desiccated thyroid. There may be cumulative effects or delay of the maximum response, as well as irregularities in the response and gradually acquired tolerance. The effect of single intravenous doses of thyroxin on the basal metabolic rate of myxedematous adults has been reported by Boothby and associates (19). The rise of the basal metabolic rate was so constant that this method was used by Salter, Lerman, and Means (147) for assay of thyroxin and other thyroid preparations. It has also been demonstrated (169) that the hypothyroid patient differs in sensitivity depending upon his basal rate; the lower the rate the greater the effect produced.

Wilkins and associates (189) determined the serum cholesterol in 9 hypothyroid children following a single intramuscular injection of 2 or 5 mg. of thyroxin. They used this method because they found no difference between the response to an intravenous or intramuscular injection. Similar studies were made on one normal child, five dwarfs, and seven other children of normal height and weight and without evidence of endocrine disorder. The cholesterol was determined in a control period, then every 3 to 5 days for 40 to 60 days after thyroxin injection, until the cholesterol had returned to the preinjection level. In the hypothyroid children before treatment the average serum cholesterol was 356 mg. per cent; after a

single dose of thyroxin the average minimum concentration was 199 mg. per cent, a decrease of 157 mg. per cent. The decrease was evident by the 3rd to 7th day, and the 14th day was the average on which the minimum concentration was reached. After the 22nd day the cholesterol rose again, reaching the base level on the 38th day. With few exceptions the magnitude and duration of the cholesterol response was apparently the same whether 2 or 5 mg. of thyroxin were employed. The sensitivity to the drug was less in two children: in one the response was ascribed to persistence of a small amount of thyroid tissue; in the other, to previous thyroid medication. In the other 11 children the injection of thyroxin caused a decrease of serum cholesterol which varied from 121 to 185 mg. per cent and lasted from 32 to 57 days. In one case of severe untreated cretinism the decrease in cholesterol lasted 71 days.

In the control group the injection of 5 mg. of thyroxin caused the serum cholesterol to fall 16 to 47 mg. per cent, with an average of 31. In the normal children the effect of thyroxin was transient. The lowest point was reached between the 3rd and 6th day, and the cholesterol returned to the basal level between the 6th and 13th day. For the 5 normal children in whom the basal rate could be determined satisfactorily, the increase varied from 21 to 36 per cent, the maximum rate being observed from the 2nd to 6th day. The rate had returned to normal by the 6th to 17th day. Dwarfs responded in the same way as normal children. The workers concluded that the single injection of thyroxin may serve to differentiate the hypothyroid from the normal child, even when both have similar cholesterol concentrations before injection.

Wilkins and Fleischmann (190) also studied the effect of discontinuing thyroid medication. They found, as did others (29, 62, 67), that the serum cholesterol in the hypothyroid child usually rose to high levels within a period of 8 to 12 weeks and that many children reached values higher than those observed before treatment was begun. No similar rise occurred in normal children. At the time thyroid medication is withdrawn, both the normal child and the child with thyroid deficiency may have identical normal cholesterol values. The rise of the serum cholesterol after the withdrawal of thyroid is, therefore, of practical diagnostic value, especially in hypothyroid children who have been treated elsewhere and have lost the stigmata of the disease. If the diagnosis is open to question, thyroid medication can be discontinued and the cholesterol can be determined for a period of two or three months. There is a definite rise in cholesterol long before clinical signs have returned in the hypothyroid child.

As in hyperthyroidism, the reciprocal relationship in hypothyroidism between the basal metabolic rate and the blood cholesterol level has been confirmed by some (62, 76, 190) and denied by others (36, 54, 61, 103). Since the work of Cutting, Ryland, and Tainter (38), it is now fairly well agreed that there is a relationship between these two levels when they undergo changes due to variation in the activity of the thyroid

gland or due to the introduction of thyroid substances into the body. These men collected data from the literature and added their own material, in all 205 cases, which they treated by standard statistical methods. They used the material by Epstein and Lande (47), Nichols and Perlzweig (116), Gardner and Gainsborough (54), Hinton (68), and Mason, Hunt, and Hurxthal (103), thus including authors who found an inverse relationship between the two factors as well as those who denied that such a relationship existed. They found a significant, inverse, curvilinear correlation when the two variables were plotted.

Changes in the blood cholesterol in thyroid disease are not related directly to the basal metabolic rate, but to other actions of thyroid secretion. Cutting and associates (38) raised the basal metabolic rates by the administration of dinitrophenol in 23 subjects, 7 of whom had basal rates below —15 per cent while the rest had normal metabolism. In the normal group the basal metabolism rose 25.1 per cent and the cholesterol increased $+14 \pm 6.9$ mg. per cent, a figure not statistically significant, which is in contrast to the fall of 50 mg. per cent which would be expected if the rise in basal metabolism were due to increased thyroid activity. In those patients whose initial basal metabolic rate was below —15 per cent, the average rise after the administration of dinitrophenol was 35.1 per cent and the cholesterol fell -8 ± 11.8 mg. per cent, which again is not statistically significant and which is in contrast to the fall of 100 mg. which would be expected if the increase in basal metabolism were due to thyroid secretion.

The thyroid is not responsible for all conditions of disturbed metabolism, for example hypometabolism, excluding myxedema. The incidence of this latter disease is comparatively low, varying from 0.01 to 0.08 per cent in large numbers of patients (79). A basal metabolism within the normal range does not necessarily exclude myxedema, and subnormal metabolic rates are normal in some individuals, as found by Boothby and associates (18).

In the absence of thyroid disease the relationship between the basal metabolic rate and blood cholesterol is far from definite. However, if hypercholesterolemia is a fairly constant accompaniment of thyroid deficiency, low basal metabolic rates, or hypometabolism, without increase in cholesterol must depend on factors other than the thyroid hormone.

Since about two-thirds of myxedematous patients are overweight (74, 77), it is logical to consider that obesity may be associated with thyroid deficiency even though clinical symptoms of myxedema are concealed (74). In a series of 24 cases of obesity Hurxthal (77) found, with the exception of one patient who had a basal rate of +24, that the metabolism varied between —10 and —24 per cent. Twelve of these cases were below —10 per cent. The cholesterol level varied from 111 to 248 mg. per cent, suggesting that most cases of obesity are not of thyroid origin, even though the basal metabolic rate is low. Still, thyroid deficiency should be considered in every case of obesity. This can be accomplished by determining the cholesterol

and basal metabolic rate, and by careful evaluation of clinical symptoms and signs. If hypercholesterolemia is found, a concealed or associated myxedema may be present, and a therapeutic test with thyroid is indicated.

The interrelation of the glands of internal secretion suggests the possibility that disturbances of the thyroid gland are secondary to dysfunction of other glands, especially the pituitary and adrenal. The functional capacity of the thyroid may be measured by the effect on the basal metabolic rate and the cholesterol concentration in the blood after the administration of the thyrotropic hormone of the anterior pituitary gland. It has been found that in normal individuals and in patients free of thyroid disease, the basal metabolic rate increases after the injection of this hormone (45, 149, 152, 163, 168), while in postoperative myxedema the thyrotropic hormone has no effect (149, 152, 163, 168). In mild myxedema the response to the administration of thyrotropic hormone approaches that of a normal individual (163, 176). After the injection of thyrotropic hormone in normal children Wilkins and Fleischmann (191) observed a decrease in the concentration of serum cholesterol of 40 to 80 mg. per cent, a value within the range of spontaneous fluctuation in a normal child. Where thyroid medication caused a decrease in the cholesterol level of the hypothyroid child, the thyrotropic hormone had no effect. In dwarfs who were not cretins, the response was the same as in normal children. If, as occasionally happens, thyrotropic hormone arouses a response in a myxedematous patient, it indicates that the thyroid gland is present and capable of stimulation.

This also suggests the possibility that the thyroid deficiency is secondary to a pituitary deficiency, which also is accompanied by a low metabolic rate (146). A deficiency of the anterior pituitary thyrotropic hormone may be responsible for this condition because it regulates the activity of the thyroid. There are, however, many differences clinically between hypopituitarism and myxedema. In pituitary deficiency the basal metabolism may be as low or lower than in thyroid deficiency, but the cholesterol as a rule is within normal limits. In 14 cases of hypopituitarism due to verified chromophobe tumors, Hurxthal (77, 78) found that the blood cholesterol in only 2 cases exceeded 240 mg. per hundred cubic centimeters of blood. There were no clinical evidences of myxedema in these patients. Therefore, while myxedema is primarily a disease of the thyroid, the low basal metabolism in hypopituitarism is not wholly of thyroid origin. Excess excretion in urine of thyrotropic hormone of pituitary origin has been reported in myxedema (6).

In suprarenal deficiency, as in Addison's disease, the basal metabolic rate is low but there is no hypercholesterolemia, suggesting that the thyroid is not at fault. This is further substantiated by the fact that in Addison's disease administration of thyroid may be harmful. However, Hurxthal (77) administered thyroid to a patient with Addison's disease, and, although the basal metabolism remained unchanged, some

stimulation was observed, i.e., a drop in cholesterol, a drop in body weight, and an increase in pulse rate. Intravenous administration of extract of suprarenal cortex raised the basal metabolism in three days.

Very little is known about the mechanism by which the thyroid hormone influences the cholesterol. It has been suggested that the variation in the blood cholesterol in thyroid disease is possibly associated with differences in the secretion of cholesterol in the bile and the excretion of this substance in the intestine. There is some evidence to show that in hyperthyroidism cholesterol excretion in the bile is increased, and in myxedema it is decreased (78). On the other hand, Boyd and Connell (23, 24, 25) and Gildea, Man, and Peters (59, 99) have shown that the cholesterol is not the only lipid which is influenced by thyroid activity, but that the decrease of cholesterol in hyperthyroidism is part of a general lipopenia, and the increase in myxedema a part of hyperlipemia. With successful treatment the lipids show changes proportionate to those of the cholesterol. Boyd and Connell (24) consequently attempt to explain the decreased cholesterol and the general lipopenia found in hyperthyroidism by either a structural or functional interference with the transportation of fat from the intestines or an interference with the conversion of the fat to cholesterol esters. The latter assumption is supported by the fact that a parenchymatous hepatitis has been found in hyperthyroid patients (182). Lichtman (94), using the cincophen test, also came to the conclusion that 16 of 20 patients with hyperthyroidism have an impaired liver function.

CHOLESTEROL IN BILIARY AND HEPATIC DISEASE

Disturbances of hepatic function are reflected by the total cholesterol concentration in the blood, as well as in the ratio of free cholesterol to cholesterol esters. This was already pointed out in 1918 by Feigl (49), who found low values of cholesterol esters in acute parenchymatous disease of the liver. The clinical significance of changes in blood cholesterol was recognized and emphasized by Thannhauser and Schaber (167): Since then practically every phase of the relationship of cholesterol to liver disease has been investigated.

There is a general agreement (1, 48, 64, 128, 167, 187) that in the majority of patients with obstructive jaundice the total amount of blood cholesterol is increased to over 300 mg. per cent, and that, as a rule the ratio of free to combined cholesterol is normal (48, 64). This increase in cholesterol is not dependent upon the agent causing the obstruction (1, 48), but there appears to be a tendency to higher values when neoplasm is the causative agent (48). When the obstruction is relieved the cholesterol concentration and jaundice decrease (1, 48, 187), although there is a tendency for the cholesterol to remain above normal for several months (48).

Epstein (48), in studying 118 cases of obstructive jaundice which were verified by operation or autopsy, found a hypercholesterolemia in 92 (78 per cent). The

highest cholesterol observed was 1500 mg. per hundred cubic centimeters of blood. The jaundice varied in intensity up to an icterus index of 160 units, but no definite correlation could be established between the cholesterol concentration in the blood and the intensity of the jaundice. The cholesterol ester was raised proportionally in 86 patients (73 per cent) and absolutely in an additional 10 per cent. With the relief of the obstruction the proportion of cholesterol ester remained constant during the decrease of the total cholesterol.

One fourth of the patients with proved obstructive jaundice do not follow the above pattern. Often hypercholesterolemia is absent (1, 48) and the cholesterol ester is below normal (48, 64). Some of these cases cannot be explained; in others the low value of the total cholesterol and the decrease of cholesterol ester are explained by complications such as infection and damage to the liver parenchyma (1, 48, 64, 167). Undernutrition and cachexia apparently do not enter the picture, since the increase of cholesterol in obstructive jaundice remains in spite of the high-grade cachexia often seen in carcinoma (1).

In acute parenchymatous diseases of the liver, including yellow atrophy, the changes in the blood cholesterol are practically opposite to those described above. The total blood cholesterol remains normal or declines. The ester fraction falls in proportion to the severity of the disease, often disappearing from the blood entirely in rapidly fatal cases (1, 26, 48, 167, 187). This lowering of the cholesterol esters in parenchymatous hepatic disease, the so-called "Estersturz" of Thannhauser and Schaber (167), is associated with a general lipopenia in nonobstructive jaundice. Boyd and Connell (26) in 27 cases of parenchymatous liver disease found in addition to the decrease of the cholesterol ester, a marked lowering of the phospholipoids and a slight decline in total cholesterol and the neutral fat.

Epstein (48) studied 130 jaundiced patients who had no evidence of obstruction. Jaundice in these cases was caused by a diffuse parenchymatous hepatic disease which in turn was caused by a variety of agents such as drugs, toxins, severe infections, and catarrhal jaundice. He found that although the icterus was intense, the total blood cholesterol was raised above 300 mg. per cent in only 12 per cent of the cases. Thus the parallelism between the icterus and the cholesterolemia seen in obstructive jaundice is absent in patients with jaundice due to parenchymatous disease. In those cases with the lowest cholesterol values and the most intense icterus the clinical condition was proportionally more severe. In 15 additional cases of atrophy of the liver the total cholesterol values were lower than observed in any other liver disease while the icterus index was markedly increased. In occasional patients only traces of cholesterol were found.

Far more important than the decrease of the total serum cholesterol was the lowering of cholesterol ester. Epstein found that it was decreased in 70 per cent of a series of 130 patients at the onset of the disease when jaundice and acute symptoms were

prominent. The hepatic damage and the cholesterol esters seemed to run parallel. In the 15 cases with acute, sub-acute, and chronic yellow atrophy, all verified by autopsy, the outstanding feature was the depression of the cholesterol ester which remained low during the course of the disease and at times practically disappeared from the blood. In 30 per cent of the patients with acute liver degeneration, the relation of the free to the total cholesterol was not disturbed. Although the reason for this is not clear, it may possibly be explained by the fact that the disease was mild or that some patients were already in the healing phase when they were first seen. Some cases may have had cholangiolitis without essential liver damage. Consequently in evaluating cholesterol determinations, especially single ones, it is important to take into account the clinical course and interpret the values in relation to the phase of the disease.

The behavior of blood cholesterol in atrophic cirrhosis (Laennec's type) varies depending upon the presence or absence of jaundice. Epstein (48) in observing 35 cases, 18 of which were confirmed by necropsy, found that the cholesterol partition was practically within normal limits in 24 patients in whom the portal obstruction predominated, but who had no jaundice. There was, however, a tendency toward slightly elevated total cholesterol and slightly diminished ester values. In 11 cases with jaundice, the cholesterol behaved as in primary degeneration of the liver, i.e., the total cholesterol failed to rise with the bilirubinemia and the cholesterol ester was lowered, especially if jaundice persisted. Thus in uncomplicated atrophic cirrhosis the liver function remains normal but with the development of jaundice it becomes impaired, and this is reflected in the cholesterol partition of the blood. Since White, Deutsch, and Maddock (187) found normal cholesterol ester values in about half of the fatal cases of liver disease, the test gives but little information in cases such as portal cirrhosis and cancer. It must be borne in mind that test may be modified not only by the kind of liver disease, but also by its acuteness or chronicity, and the presence or absence of infection. The amount of damage also may be effectively masked in chronic liver disease by regeneration. This may explain normal cholesterol values in some cases (187) since there is a strong tendency for the usually stable cholesterol metabolism to return to normal after an acute disturbance.

It has been generally assumed that the liver regulates the cholesterol level of the blood and its partition into free and ester fractions (48). However, the mechanism causing the disturbance in the cholesterol concentration in liver disease has not been satisfactorily elucidated. In obstructive jaundice it was formerly assumed that the increase of blood cholesterol was due to interference of excretion through the bile, in effect a mechanical obstruction. More recent investigations reviewed by Bloor (14) and Weinhouse (180) have shown that bile cholesterol is completely absorbed and that the main pathway for excretion is the lower intestine. The cause of hypercholesterolemia in mechanical obstructive jaundice thus remains un-

known, as there is no evidence to support the theory that changes in cholesterol are due to disturbed absorption of fat.

In degeneration of the liver parenchyma loss of the function of esterification may account for the low blood values (167). Another theory about the mechanism which causes a decrease in cholesterol esters in parenchymatous liver disease has been expressed by some investigators who believe that when liver cells are broken down a liver enzyme, cholesterol-esterase, which splits cholesterol esters under normal conditions, is set free and then splits the cholesterol esters, thus causing a decrease of the latter in the blood (48, 180).

Prognostically cholesterol determinations are considered of distinct clinical value (48, 64, 128) although White and associates (187) found that determinations of total cholesterol concentration gave but little information. Hypocholesterolemia in liver disease is usually unfavorable, and a decrease in the percentage of cholesterol esters, regardless of the amount of total cholesterol in the blood, serves as an index of the degree and severity of hepatic damage in acute parenchymatous liver disease such as catarrhal jaundice, acute yellow atrophy, and toxic hepatitis even though the extent of liver involvement cannot be gauged. However, a steadily dropping cholesterol ester or a persistently low value in patients with jaundice is an ominous sign, regardless of the clinical condition at the time the determination is made. High figures show a mild disturbance only. Conversely, the improvement in parenchymatous degenerative liver disease is heralded by an initial increase in cholesterol ester and followed by an increase in the total cholesterol level to normal or above normal. This hypercholesterolemia often persists for months (48).

In obstructive jaundice, on the other hand, a decrease of cholesterol together with the bilirubinemia indicates improvement. At times a decline in cholesterol and a disturbance in the ratio of free to combined cholesterol in biliary surgical disease indicate complications, such as infection and parenchymatous damage, even though there is no jaundice (64). It has been found that patients with low cholesterol values and a disturbed cholesterol partition are poor operative risks, while those with normal cholesterol partition in the blood make uneventful recoveries (64, 128, 187). It is not only useless but dangerous to operate on patients with acute disease of the liver during the height of the attack. Frequent determinations of cholesterol esters for the purpose of evaluating liver function, therefore, are desirable. Pickhardt and associates (128) suggest that patients who exhibit a low functional reserve of the liver should be treated medically preoperatively and that repeated cholesterol examinations should be made to determine whether the functional reserve has returned to normal. Such information is of value in surgery of the biliary tract and serves to indicate the optimum time for surgical intervention. Occasionally in combined obstructive and parenchymatous jaundice, the total cholesterol values may be above normal while the esters are reduced. The reduction of jaundice in such cases gives a false se-

surity regarding the operative risk (64).

From the diagnostic point of view, repeated determination of both the total cholesterol concentration and the cholesterol partition may be of particular value in differentiating obstructive from non-obstructive jaundice, since the behavior of the blood cholesterol is practically opposite in these two types of jaundice. In obstructive jaundice with parenchymatous damage, cholesterol determinations are of little value in differential diagnosis (128), and occasionally the cholesterol is elevated in toxic hepatitis. However, a jaundiced patient with known gallstones and suspected obstruction probably does not have obstructive jaundice if the blood cholesterol concentration is normal.

As with all laboratory examinations, cholesterol concentration in the blood must be fitted into the clinical picture and correlated with all other data bearing upon the disease.

CHOLESTEROL AND GALLSTONES

The problem of gallstones is essentially that of precipitation of cholesterol in the bile, because a large series of the common mixed and combination stones has been found to average 94 per cent in cholesterol content (127). The solitary cholesterol stone contains from 98 to 99 per cent. The remainder is calcium salts and bile pigments, and traces of fatty acid. No bile salts are present. Pigment stones and calcium carbonate stones are rare in man.

It is evident that the large cholesterol content of biliary calculi should suggest some disturbance of the cholesterol metabolism, and many theories have been advanced to explain the formation of gallstones and the mechanism of the precipitation of cholesterol.

As the cholesterol in the bile presumably is manufactured from the blood and excreted by the liver in the bile, the theory of hypercholesterolemia as a causative factor of gallstones has held a prominent position. In addition, dysfunction of the liver or functional or pathological changes in the biliary ducts and the gallbladder may alter the composition of the bile and facilitate the precipitation of cholesterol and other constituents.

The view that hypercholesterolemia and increased excretion of cholesterol in the bile is the fundamental cause of cholelithiasis has been ardently advocated by Chauffard, Aschoff (7), Boyd (28), Judd and Mentzer (86), Whitaker (185), and many others have assumed that at least the pure and often solitary cholesterol stone is of metabolic origin and depends upon the correlation of an elevated blood and bile cholesterol. The same assumption has been made for cholesterosis of the gallbladder (strawberry gallbladder), a condition in which the mucosa of the gallbladder contains an excessive amount of cholesterol. Cholesterol or cholesterol esters are held in the surface epithelium or just below the mucosal covering in the phagocytic cells connected with the reticulo-endothelial system. Often the amount is large, and small-to-large polypoid masses project from the mucosa. Occasionally these polypoid masses are separated and furnish the nucleus for a calculus (28). It is a relatively common disease.

Mentzer (108) in a series of 12,499 surgical gallbladder specimens found 22 per cent, and in 1674 consecutive autopsies 37 per cent with cholesterosis. Stones accompanied the lesion in less than half of the surgical cases and in about two-thirds of the gallbladders examined postmortem.

In a study of 2742 cholecystectomies for cholesterosis (108) it was found that the Graham-Cole roentgenograms indicated that the gallbladder mucosa was capable of concentrating the dye normally in mild, and occasionally in advanced, stages of the disease. The gallbladder in this disease, in Mentzer's opinion, is apparently only an indicator of a generalized metabolic fat disturbance. The lipoid accumulates in the gallbladder wall either as a result of a local disturbance or because of the generally increased cholesterol content of the body. Gallstones as a rule are not a significant accompaniment of this disease and the clinical picture is not essentially modified by their presence.

The mechanism of deposition of cholesterol in the gallbladder has been thought to be due to either a secretion or an absorption of the gallbladder mucosa or to a degeneration of the same. Elman and Graham (46) from experimental evidence hold the view that the gallbladder secretes cholesterol and that this process is accelerated when infection is present. Whenever the bile for one reason or another becomes unable to take up any more, the cholesterol remains in the mucosa and the wall. Other investigators (8, 28, 40, 106, 126, 185) hold that cholesterol is absorbed rather than secreted from the mucosa, although the deposition of excess cholesterol from the blood cannot be excluded (7). Whitaker (185) concludes that cholesterosis is a metabolic fat disturbance with hypercholesterolemia and a tendency of the entire reticulo-endothelial system, including the gallbladder, to take up the excess cholesterol. In addition, the liver secretes a bile high in cholesterol content and probably with insufficient bile salts to hold it in solution. If there is stasis of the gallbladder, the precipitated cholesterol particles are taken up by the mucosa and are phagocytosed by the histiocytes which collect in large masses and produce the typical strawberry seed polyp.

The role of inflammation in cholesterosis of the gallbladder is considered by some to be of primary importance, while others assign it to a secondary position. Boyd (28) found an inflammatory process in every case of cholesterosis although it was seldom marked. He suggests that if cholesterol should chance to be absorbed from the bile and pass into the gallbladder wall, any inflammatory process which interferes with absorption may result in a deposition of cholesterol first in the surface layer and later in the deeper coats. If it is assumed that the villi are especially concerned in absorption, the cholesterol deposit, as a matter of course, would be most pronounced in these structures. Often, however, the inflammatory process is slight and seems of doubtful significance (107). Whitaker (185) suggests that the inflammatory reaction is secondary and may be a result rather than a cause of cholesterosis. The lipoid material in the

phagocytes may act as a mild irritant inciting an inflammatory reaction, a phenomenon seen in many other tissues containing phagocytes with ingested material.

In support of the theory that hypercholesterolemia is the fundamental cause of cholesterosis as well as cholelithiasis is cited the well-known fact that pregnancy is physiologically associated with a moderate hypercholesterolemia and that there is a high incidence of biliary calculi during and after gestation. Judd and Mentzer (86) in a study of 1000 cases of cholesterosis of the gallbladder, with and without stones, found that it is predominantly a disease of the female with an incidence of 76 per cent of the stone-free and 82 per cent of the gallstone cases. Of these women with cholesterosis 58 per cent without, and 67 per cent with stones had been pregnant one or more times, and 45 per cent dated their symptoms to the first pregnancy. In 30 per cent of the 500 cases with stones, the stones were single, and in 99 per cent of the cases the stones were of the cholesterol-rich type. This, in their opinion, lends support to the theory that cholesterosis of the gallbladder is primarily a metabolic disease, and a localized manifestation of a disturbed fat metabolism in the entire body.

The relation of hypercholesterolemia and cholesterosis of the gallbladder was studied by Mentzer (108) in 200 cases. He found an appreciable increase over the normal in almost every case, but the patients had to be examined frequently over long periods of time. Riegel and associates (140), in a study of 34 specimens of gallbladder bile, removed from living women at term during Caesarean section, concluded that in pregnancy both the composition of the liver bile and the absorptive function of the gallbladder are changed from normal. The viscous was distended at operation, and in general the cholesterol concentration of the gallbladder bile was increased. In every instance the bile salt concentration was below the normal, a condition favoring the formation of calculi. Boyd (28) points out that the formation of gallstones depends upon a variety of circumstances which apparently are periodic. A collection of stones from a single case seldom show a great variation in size and type. The stones are, as a rule, of the same size as if they had been formed at the same time and there may be a variation of one set as compared with another. Infection and the cholesterol content of the blood and bile during pregnancy are the two factors most liable to periodic fluctuations. Fox (51), however, found no increase of bile cholesterol in pregnancy and Campbell (33) states that although the blood cholesterol is increased in pregnancy, the bile cholesterol is decreased, an observation which was interpreted by an early observer (66) as due to retention of cholesterol.

On the assumption that the pure cholesterol type of gallstone is metabolic in origin, it would seem logical to suppose that in diabetes, in which, before intensive insulin treatment, a hypercholesterolemia was usually present, the pure cholesterol type of gallstone might predominate, and that, in addition, the hypercholesterolemia might be associated with an increased

incidence of gallstones in this disease. From studies by Gross (65), Hunt and DeFrates (72), and Joslin (85), it is evident that there is a connection between diabetes and gallstones. Joslin states that gallbladder stones are more common in diabetics than in the general population of the same age group, although cholelithiasis in these patients is apt to be mild. Although Gross found a higher incidence of the solitary cholesterol and faceted stones in diabetics than in a control group of nondiabetics, Hunt and DeFrates (72) could not prove this point.

The obesity of many of the patients suggests additional evidence in favor of the metabolic origin of biliary calculi, at least of the pure cholesterol type, and cholesterosis. Judd and Mentzer (86), in their study of 1000 cases of cholesterosis, observed that 21 per cent of the stone-free and 33 per cent of the gallstone cases weighed more than 175 pounds. Statistics also show that gallstones in general are more likely to occur in fat persons (65, 107) and in proportion to their obesity. Aschoff (7) believes that the rapid loss of fat in the course of treatment for obesity as well as the diminished elimination of cholesterol by the breast of non-nursing women may lead to the formation of pure cholesterol stones. He considers it probable that cholelithiasis is at least partly concerned with an abnormal fat or cholesterol metabolism in the organism and may be related to arteriosclerosis and allied conditions. Gallstones, however, are twice as common in women as in men. This difference in sex incidence is not, according to Gross (65), wholly, or even mainly, ascribable to the influence of pregnancy since gallstones are not appreciably more common in married than in single women. If the statistics of Gross are confirmed, then some factor other than pregnancy must be found to explain the definitely greater female tendency to cholelithiasis.

Interestingly enough, in subacute parenchymatous nephritis or nephrosis, where hypercholesterolemia of considerable proportion is the rule over long periods of time, Gardner and Gainsborough (55) found no evidence that such hypercholesterolemia favored the formation of gallstones.

Even though it has been generally conceded that the solitary pure cholesterol stone is of metabolic origin, the theory of hypercholesterolemia and increase of bile cholesterol in cholelithiasis with mixed or combination stones has not only been refuted in the more recent work but the actual facts have been questioned by Campbell (33) who found the amount of cholesterol in the blood to be within normal limits both in cholelithiasis and cholecystitis when the patient was not jaundiced. This has lately been verified by Carter and associates (35) who, in a study of 239 patients with and without gallstones but with disease and dysfunction of the gallbladder, came to the conclusion that the level of blood cholesterol apparently did not play a role in the causation of stones, since preoperative and postoperative cholesterol levels were remarkably equal in the whole series. Hypercholesterolemia was found almost as often in patients with stones as in those without (29 per cent and 20 per cent re-

spectively). Moreover, the general level of blood cholesterol in these patients was normal.

Considerable difficulty has been experienced in the study of the bile and its relation to the blood cholesterol concentration under physiological conditions. Bile in man must be obtained either from a diseased gallbladder at operation, from fistulas, or from postmortem material. As it has been shown (1-3) that the amount of cholesterol in the blood, in the liver, and in the bile is enormously increased by starvation and may be tripled in a short time, this fact must be remembered in studies of bile cholesterol on postmortem material. In most of the surgical specimens obtained, the pathological changes in many instances have passed, gallstones representing the end result of the pathological process, and there is no way of ascertaining what the blood or bile cholesterol was at the time the stone was formed. Carter and associates (35) found that the composition of the hepatic bile and that obtained by duodenal drainage as well as gallbladder bile at the operation was not related to the chemical composition of the blood. Fowweather and Collinson (50), however, claim that hypercholesterolemia is typically present in the acute stage of the disease responsible for gallstone formation and that it disappears with the passing of an acute attack. Hypercholesterolemia in their opinion indicates the presence of a recent attack of the disease, not gallstones or cholecystitis. They suggest that the varying and contradictory findings with respect to hypercholesterolemia in cholelithiasis may simply be due to the fact that the examinations have been made at various stages of the disease. In their cases 40.7 per cent showed a definite increase of blood cholesterol and 44 per cent an increase of bile cholesterol. Fox (51) from the collected data of several observers, found that fistula bile contains from 42 to 95 mg. of cholesterol per 100 cc., with an average of 57 mg. Bile obtained from both normal and pathological gallbladders varied from 160 to 790 mg. He obtained a range of 290 to 914 mg. per cent in three accident cases. Thus the cholesterol content of the bile from pathological gallbladders did not differ significantly from normal ones, and both classes showed great variability. Therefore Fox feels that any differences observed by various investigators have been well within the range of normal variation.

The clinical significance of cholesterol in cholecystitis and cholelithiasis is of peculiar importance because of the established treatment of this disease. On the assumption that hypercholesterolemia is the cause of cholelithiasis, fats and cholesterol-rich foods have been excluded from the diet in the belief that dietary control may reduce the incidence of stone. Several observers (105, 110, 174, 175, 185) claim that the blood cholesterol concentration can be thus controlled while others (33, 35, 39, 51, 63) have been unable to demonstrate a significant change. However, even if a long-range diet may increase or decrease the concentration of blood cholesterol somewhat, there is so far little evidence available that either diet or blood cholesterol influences the bile cholesterol. Studies by Fox (51), Gardner and Gainsborough (55), and subse-

quent observers (3, 39, 63) support the theory that ingested cholesterol does not appear in the bile and that diet has no influence. They disclaim a correlation between blood and bile cholesterol and any relation between blood cholesterol concentration and biliary calculi. Clinical observations by Gough (63) have also shown that in patients with bile fistula who have normal basal metabolic rates, diets high or low in cholesterol cause a variable concentration of cholesterol in the bile and no change in the blood concentration. The study of the available facts concerning the cholesterol metabolism, therefore, makes it clear that therapeutic measures as practiced are physiologically unsound and based on pure assumption since no one has succeeded in demonstrating that diets of different cholesterol content have any effect on the bile cholesterol (12, 55, 63, 114, 184). The validity of hypercholesterolemia as a causative factor of cholelithiasis rested on the belief that the liver was the main excretory organ for cholesterol and that a high blood cholesterol, *a priori*, was associated with a high bile cholesterol with subsequent precipitation of this substance as biliary calculi. This misapprehension has been dispelled by the work of Sperry (159), Beumer and Hepner (12), and Schoenheimer and von Behring (150), who have shown that the main excretory organ for cholesterol is the lower intestine, not the liver.

Since the attempts to explain cholelithiasis in general by hypercholesterolemia have met with but little success, other theories have been advanced. Newman (115), and Andrews and associates in a series of papers (2, 3, 4) have stressed the fact that cholesterol is held in solution, and probably in colloidal dispersion, by the action of bile salts. A definite ratio may be essential to prevent crystallization, and a disturbance of this ratio is probably the first step in stone formation. According to Newman (115) the normal ratio is 25:1 and the critical ratio 18:1, while Andrews and associates (4) placed the critical ratio at 13:1. The factors which may be of importance in changing the ratio of bile salts to cholesterol may be sought, in addition to changes in the cholesterol concentration of the blood, in dysfunction of the liver, or functional or anatomical changes in the biliary passages and the gallbladder.

It has been demonstrated that bile salts are secreted by the hepatic parenchyma and that their excretion is an index of liver function (184). Any disturbance of the liver function, consequently, may lead to a change in the bile salt concentration in the hepatic bile. Smyth and Whipple (157) have shown experimentally that certain liver poisons, such as chloroform in small doses, incapable of causing recognizable histological changes in the liver cells, can effect a profound decrease in bile salt concentration in fistula bile. It has also been demonstrated that altered hepatic secretion favors precipitation and gallstone formation (145). In liver disease of man, Andrews, Hrdina, and Dostal (3) found that the liver secreted bile of lowered bile salt-cholesterol ratio. Judd and Mentzer (86) at operation in almost 90 per cent of their cases found gross hepatitis associated with gall-

bladders obviously inflamed and containing deeply pigmented common stones. Intermittent obstruction or stasis of the bile in the gallbladder probably causes damage to the liver which in turn may cause the output of an unstable bile favoring the precipitation of cholesterol. There are also many different factors involved in rapid changes in the amount and kind of fat content of the liver. Any considerable increase, even if produced by physiologic means, impairs the organ with regard to its function (102, 138). In this connection it is interesting to speculate about the relation between obesity and cholelithiasis.

Andrews, Hrdina, and Dostal (3) in their studies did not find changes in the bile salt-cholesterol ratio in the liver bile of sufficient magnitude to approach the critical level of precipitation. In their opinion the responsibility for gallstone formation seems to lie in the gallbladder itself rather than in the liver.

It is fairly well established that the normal gallbladder concentrates the hepatic bile by absorption of water and inorganic salts, and differs from the liver bile only in concentration. The degree of concentration is limited by the fact that the gallbladder empties after meals and consequently depends upon the time the bile remains in the gallbladder (137, 144). This factor itself may favor crystallization. If, in addition, there is a complete or partial failure of expulsive action in the muscular coat, stasis of varying degree is produced. If the bile from the liver is abnormal to start with, such a condition may lead to the formation of gallstones (185). From experimental and clinical studies (39) it would also appear that the gallbladder, not under normal conditions but in the presence of inflammation, absorbs bile salts and cholesterol. Andrews and associates (2) found that in normal gallbladders removed surgically the ratio of bile salts to cholesterol was 25 to 1 while in diseased gallbladders the ratio was 2.5 to 1. In their opinion these observations offer definite proof that the diseased gallbladder absorbs bile salts more rapidly and at the expense of cholesterol. Furthermore, in all gallbladders in which the cystic duct has been obstructed for long periods, all the bile salts have been absorbed and the cholesterol is present in crystalline form. Stasis alone will not bring about absorption of bile salts; the factor of infection is the important one. Andrews and co-workers, therefore, concluded that the actual cholesterol content in the bile is not so important in gallstone formation as the ratio of cholesterol to the substance that holds it in solution (3). Doubilet and Colp (41) confirmed that the ratio of bile salts to cholesterol is lowered in the bile of the gallbladder with concretions. Carter and associates (35), on the other hand, comparing the composition of bile from calculous and noncalculous gallbladders found that in nearly 80 per cent of all, noncalculous cases the concentration of bile salts in the bile was below that ordinarily considered necessary to keep cholesterol in solution and yet stones were not formed. Among the cases of calculus, the ratios in 14 per cent were sufficient to keep cholesterol in solution and in 22 per cent it was above 13:1. They concluded that

while bile salts may help to keep cholesterol in solution, changes in this purely chemical factor could not be held accountable for the stones seen in their series.

Another view is held by Riegel, Ravidin, and Johnston (139). From their studies they concluded that dilution rather than concentration of bile occurred as a result of injury to the gallbladder. This dilution lessens the solvent effect of bile salts on cholesterol (11).

There is considerable controversy as to the role of infection in cholelithiasis and whether it precedes the calculi or is caused by them. Whitaker (185), from his work, came to the conclusion that the direct causation factor is not the infection as such but the inflammation in the gallbladder wall which interferes with its function, including stasis and altering the chemical composition of the bile. He emphasizes the factor of stasis as essential to gallstone formation regardless of the condition, functional or organic, producing the stasis. Others have agreed with him (35). If the gallbladder functions normally, it empties itself more or less completely after meals, especially if fats are included (158), and there is little opportunity for collection of debris since the vesicle is effectively flushed several times a day by the influx of fresh bile. A necessity for stone formation is a lack of bile which is furnished by stasis or obstruction in the ducts or the gallbladder.

The treatment of cholecystitis and cholelithiasis by a diet low in fat thus violates another physiologic principle. According to Ivy (80) the contraction and the emptying of the gallbladder is induced by cholecystokinin, a hormone elaborated in the presence of fatty substances when it touches the mucous membrane of the duodenum. In addition, the sphincter of Oddi is relaxed by substances such as ordinary fat and various chemicals, the best known being magnesium sulphate. Ivy (81) reports that the frequent administration of egg yolks and cream augments the rate of passage of sand placed experimentally in the gallbladder of the dog. Thus if the formation of bile is normal, frequent evacuation facilitates the removal of sediment from the viscera. Withdrawal of fatty substances, especially egg yolk, cream, and butter from the food, besides furnishing an unpalatable and monotonous diet low in fat-soluble vitamins, removes the physiological stimulus, thereby promoting gallbladder stasis. Gardner and Gainsborough (55) state that no theorizing about the amount of cholesterol in the bile can possibly justify the latter treatment. Actually, therefore, instead of reducing the fat intake, these patients should be given fat in the form of cream or olive oil between normal regular meals restricted in amount to promote physiologically the evacuation of the gallbladder (114). Musser (114) observed that a number of patients do not have an intolerance to fat and that some do not do well on low fat diets. Clinically, olive oil sometimes relieves the dyspepsia associated with this disease (63, 114). Jenkinson (82) advocates a high fat diet in conjunction with decholin to promote evacuation in patients with cholecystitis, especially those who present a gallbladder with a negative cholecystographic re-

sponse upon administration of tetraiodophenolphthalein.

There appear to be a multitude of factors which contribute to the formation of gallstones. The ratio of bile salts to cholesterol is probably one of them. The effect of inflammation on the gallbladder, and other lesions of the liver and biliary passages, on the constituents of the calculi, and the physiologic function of the gallbladder causing stasis undoubtedly are operative in many instances. Metabolic factors connected with fat, especially the cholesterol metabolism, probably play a role. It is difficult to evaluate their precise position, and as Carter and associates (35) have pointed out, it is not possible to determine the cause and pathogenesis of gallstones solely by a study of the patient at the time of operation. The deposition of the calculus may depend on several factors and the period of calculus formation may be limited. A study of a patient with stones of many years' duration, therefore, will not present the true picture of the conditions operative at the time the stone was formed.

Some suggestive experimental data have recently been published by Okey (118) which may prove to be of significance in the pathogenesis of gallstones. In dietary experiments on guinea pigs the addition of riboflavin and pantothenate to basic diets with and without 1 per cent cholesterol initially increased the well-being of all the animals fed the basal diet plus the cholesterol, then subsequently showed an abrupt and usually fatal anemia without previous signs of illness. Eighty per cent of these fatal cases revealed gallstones rich in calcium phosphate and with some cholesterol, which were accompanied by irritating lesions of the gallbladder and biliary passages. An additional 15 per cent showed "murky" bile but no stones. Control animals were free of stones. The conclusion seems inevitable that an overabundance of vitamin B will lead to gallstone formation in animals otherwise tolerant to cholesterol-rich diets.

CHOLESTEROL IN DIABETES

Hyperlipemia is a frequent finding in untreated or uncontrolled diabetes and in the pre-insulin era, increase of fat in the blood was a characteristic finding (85). This is not a derangement of the cholesterol metabolism alone, but of fat in general, mainly the neutral fat fraction. Whenever the fat is increased in the blood the cholesterol is increased and, conversely, both fat and cholesterol decrease simultaneously in this disease even though the cholesterol does not keep pace with the neutral fat. From the clinical point of view, however, it has been found that cholesterol is a good index of the fat metabolism (71). It is also more easily determined than the total fat.

The mechanism by which hyperlipemia is produced in diabetes has not been fully elucidated, but Campbell (34) has suggested that whenever there is a continuously greater demand for fat as fuel because of the lack of available carbohydrates, the result is an increase of blood fat. When more carbohydrates are utilized the lipemia tends to subside.

Blood cholesterol as a measure of total lipids in diabetes indicates, when high, a serious derangement of fat metabolism usually coincident with a low carbohydrate tolerance (89, 186). This holds true for both children and adults. When cholesterol values over 400 mg. per cent are found in diabetic patients, it usually indicates some serious complication, such as acidosis or coma (85, 100). However, there is no direct relationship between the blood cholesterol concentration and the degree of acidosis. In Hunt's series (73) about 50 per cent of the coma cases had cholesterol values which were normal or slightly above normal at the height of the acidosis, and only 5 per cent had markedly elevated cholesterol values which did not return promptly to normal with therapy. When extremely high cholesterol concentration occurs during coma, it does not carry a prognosis any worse than that for all cases of acidosis (73, 100). Mai and Peters (100) demonstrated that the concentration of cholesterol in their 15 patients with coma, when corrected for the hemoconcentration, was seldom above the normal limit at the height of the acidosis and was often below these limits at the end of the recovery period. They examined their patients frequently during the recovery from diabetic acidosis, and they emphasize the similarity in the behavior of total proteins and cholesterol in the serum and the independence of variations in cholesterol and nonphospholipid fatty acids. Hypercholesterolemia, if adequately treated, is usually of short duration in patients with diabetic coma.

In diabetic patients who do not have acidosis cholesterol concentration above 400 mg. per cent is more serious because it represents a permanent rather than a transient state of high blood fat. In 2200 selected diabetics from Joslin's clinic, studied with regard to cholesterol over a 10-year period, only 93 were found whose values exceeded 400 mg. per cent, and 68 of these had high cholesterol apart from acidosis and coma. Of these latter cases, 22 were children with diabetes which began in infancy. Most of these 68 patients had complications such as cataract and abscesses and a tendency toward deposition of cholesterol in the tissues as seen in lipemia retinalis, atherosclerosis, and xanthoma diabetorum (166).

The lack of parallelism between blood cholesterol concentration and the degree of acidosis is also observed when the blood cholesterol and blood sugar levels are compared. Hunt (73), in a group of 43 patients with an average cholesterol value of 557 mg. per cent, found that the average blood sugar was only 240 mg. per hundred cubic centimeters of blood. Likewise Rabinowitch (130) observed that the incidence of complications was high in patients with increased blood cholesterol even though the blood sugar was normal and glycosuria absent. Dietary indiscretion in such patients resulted in hyperglycemia which was controlled with difficulty by insulin and diet.

A normal blood cholesterol is observed, as a rule, in the insulin-treated diabetic patient, indicating that the fundamental disturbance of the metabolism is under control (71, 129, 186). In an investigation of 110

diabetic children White and Hunt (186) found that excess of cholesterol in the blood is an exception in uncomplicated diabetes. If lipemia is present, successful treatment with insulin and diet causes a gradual decline of the cholesterol concentration. Blood cholesterol, therefore, is considered as a measure of the progress and adequacy of treatment and is a valuable aid in the management of the disease. Rabinowitch (129) emphasizes that the blood cholesterol is a better index of the course of the disease than the blood sugar, and recommends determinations of cholesterol at intervals in the routine management of diabetics. With normal blood cholesterol concentration the patient is less likely to have complications. Therefore, a normal blood cholesterol concentration indicates a favorable prognosis (71, 129), and conversely, the higher the persistent blood fat, the more serious is the prognosis. In cases where hyperglycemia and glycosuria are controlled with difficulty, cholesterol values are of some help in judging the severity of the diabetes (133). However, the blood cholesterol concentration does not indicate whether the diabetes is mild or severe. Normal values are found when the disease is under control but as Rabinowitch (133) has pointed out, control and severity of diabetes are not synonymous terms. Blood cholesterol concentration, consequently, shows no relation to insulin requirements or carbohydrate tolerance although, as a rule, groups with mild hypercholesterolemia do not require excessive amounts of insulin. On the other hand, a patient developing acidosis and coma is not necessarily a permanently severe diabetic. A mild diabetic with loss of tolerance because of infection but with normal cholesterol values will, in all probability, still have only mild diabetes on recovery from the coma. Conversely, a patient with high cholesterol concentration who recovers from coma will probably be more severe and require more insulin, and may have a greater tendency toward complications (133). Similar conclusions have been drawn by Joslin (85) who states that, as a rule, the percentage of fat rises with the severity of the disease although the hypercholesterolemia is not directly proportional to either the severity of the disease or the rise of the blood sugar.

Comparison of data obtained during the past 25 years shows that the average blood cholesterol concentration in the diabetic patient has decreased substantially. Before 1924 the blood cholesterol averaged over 300 mg. per cent, and according to Hunt (73) the average values in 1916 were 360 mg. per cent and in 1939, 221 mg. per cent. Similar lowering of the cholesterol values in the diabetic patient has been reported from other large diabetic clinics and it has been considered as evidence of the improvement in treatment by insulin and the change in diet, particularly the more liberal allowance of carbohydrate. That this is not always true has been shown by Rabinowitch (135) who analyzed cholesterol values obtained on admission before any treatment was instituted. In 1926 the admission blood cholesterol was 348 mg. per cent and in 1933, 242 mg. per cent. Earlier diagnosis, in his opinion, is responsible for the lowering of the admission

values. Rabinowitch also found that there were significant differences in the plasma cholesterol in fully established diabetes, in the early stages, and in the potential diabetic as determined by the glucose tolerance test. Another variable in the interpretation of plasma cholesterol values is the immediate effect of treatment of acidosis and acute diabetes with high cholesterol values. As in the latter cases there is a rapid decrease of cholesterol with treatment, conclusions cannot be drawn from small series. Other factors which influence the statistical evaluation of cholesterol are infection and endocrine disturbances, especially thyroid disease. Treatment of diabetes alone obviously is insufficient for the establishment of normal blood cholesterol concentration when the above-mentioned complications are present. Man and Peters (101) consider that in treated diabetes disturbances of the fat content of the blood may be caused by complications such as cirrhosis of the liver or renal disorders, especially nephrosis. When these are eliminated, the rest of the cases with greatly elevated lipoids fall into a group that have an unstable autonomic nervous system. This is also reflected in instability of the carbohydrate tolerance and difficulty in regulation by insulin and diet.

Occasionally low cholesterol values are found in the diabetic patient. In an analysis of 2200 cases by Joslin (85), 25 were found with cholesterol values of 90 mg. per cent or less. Such patients almost always have severe complications such as tuberculosis, septicemia, pernicious anemia, pituitary disease, and diseases of the liver. These conditions are associated with severe cachexia and low cholesterol values in the nondiabetic patient and are not directly due to diabetes although it may be a contributing factor. Low cholesterol values in the diabetic patient are of grave significance. In the above series approximately 40 per cent of the cases with 90 mg. per cent of cholesterol or under, died on the average within five weeks following the determination of cholesterol.

There is no convincing evidence that insulin exerts a direct effect on the blood lipid concentration. Administration of insulin to normal men has produced no consistent results (31) and in schizophrenic patients treated with insulin a slight rise has been observed (136). The effect of insulin on the lipid metabolism in diabetes is probably an indirect one depending on the action of this substance on the carbohydrate metabolism. When carbohydrate utilization is improved, the lipemia usually subsides.

Since the introduction of insulin there has been a remarkable shift in the causes of death among diabetic individuals. Data from Joslin's clinic (85) reveal that in the Naunyn era from 1897 to 1914, abnormal fat metabolism which resulted in acidosis and coma caused the death of 63.8 per cent of the patients. In the Allen era from 1914 to 1922, 42 per cent died in coma while in the so-called Hagedorn era since 1937 death was caused by coma in only 3.6 per cent. Coma today is either an accident or carelessness. Arteriosclerosis has taken its place in diabetic mortality and according to Joslin's statistics (85)

60.4 per cent of the deaths are now due to cardio-renal vascular disease.

The reason for this shift in the diabetic mortality is partly due to the fact that in the pre-insulin era few patients with severe diabetes lived long enough to develop arteriosclerosis. With insulin therapy, the diabetic individual lives longer and arteriosclerosis has shown an alarming increase. The comparative figures compiled by Joslin show that in the Naunyn era the average duration of diabetes was 4.9 years and 18 per cent showed arteriosclerosis. In the Hagedorn era (January, 1937, to March 29, 1940), the average duration was 12.5 years and arteriosclerosis was present in 60 per cent.

Root and associates (142), in a statistical study of atherosclerotic lesions in the coronary arteries of 349 diabetics and 3400 nondiabetic patients at autopsy found that coronary occlusion in the age group from 40 to 60 was present in 23 per cent of the diabetics as compared with 6 per cent of the nondiabetic patients. Coronary narrowing without occlusion was also more frequent in diabetic than in nondiabetic patients. Significant atherosclerosis with occlusion or narrowing was absent in 49 per cent of all diabetic patients and in 82 per cent of nondiabetic patients. The coronary atherosclerosis was more advanced in patients with diabetes of long duration while absence of significant atherosclerosis was found in mild cases and those of short duration.

Disturbance of cholesterol metabolism (57, 85, 135, 142) has been suggested as the cause of the excessive development of arteriosclerosis in diabetic patients, in addition to the aging process, as evidenced by the lipemia or the increase of blood cholesterol at various stages of the disease. This view is supported by White and Hunt (186) who in a series of children with diabetes found that atherosclerosis occurred with both low and high plasma cholesterol concentration but those with a high plasma cholesterol concentration were more liable to develop atherosclerosis than those with normal cholesterol values. Shephardson (153) observed a striking parallelism between the decrease of the blood cholesterol concentration and the incidence of arteriosclerosis in young diabetics. Rabinowitch (135) did not find any difference between the average cholesterol values in a group of uncomplicated diabetics when they were simply divided according to the presence or absence of cardiovascular disease. However, when they were grouped according to age, it was found that individuals of 50 or under, suffering from cardiovascular disease had an average cholesterol of 43 mg., or 19 per cent higher than patients without cardiovascular disease. In his opinion, these data support the view that the metabolism of the young diabetic differs from that of elderly individuals in that the accumulation of lipids is more marked in the young. Man and Peters (101), on the other hand, in a series of 79 diabetic patients, found that severe arteriosclerosis, with or without hypertension, was present in patients with blood cholesterol ranging from below to above normal. The finding of normal cholesterol values in diabetes, however, does not ex-

clude the possibility that excess quantities may have been present at some time, with the development of arteriosclerosis.

According to Warren (178) hypercholesterolemia and atherosclerosis are associated. In 1930 he found arteriosclerosis present in every diabetic whose disease had lasted more than 5 years. In 1938, four cases with a duration of over five years revealed no arteriosclerosis at autopsy, indicating that the more satisfactory treatment of the disease and the control of hyperlipemia is a possible factor in the prevention of this complication. As further evidence has been cited the fact that the outstanding lesion in diabetic individuals is the atheroma of the intimal type, no matter what arteries are involved, although other types may be present. In addition the prevalence of atheroma and other lipid deposits together with large amounts of blood lipids in both young and old diabetic patients suggests a connection between the disturbance of the lipid metabolism and atherosclerosis.

The function of cholesterol in the production of arteriosclerosis, however, is still a debatable question. From the morphological and chemical points of view, cholesterol deposits have been demonstrated beyond any doubt in the atherosclerosis of the aorta and other arteries (69). Cholesterol is not only substance involved; the other lipids also participate in the proportion found in the blood plasma. The deposition of cholesterol in diabetic arteriosclerosis, moreover, differs quantitatively but not qualitatively from the nondiabetic type (91).

The question arises whether hyperlipemia with hypercholesterolemia is the primary etiologic factor in the production of atherosclerosis. On chemical grounds the evidences seem to support the view that lipids in the blood infiltrate and are deposited in the intima instead of originating in the cells of the atheromatous lesion (69). Weinhouse and Hirsch (181) suggest that the lipid deposits are the result of non-selective infiltration from the plasma. Subsequently the cholesterol increases rapidly in comparison with other lipids.

The imbibition theory of arteriosclerosis is supported by Aschoff (7) who claims that cholesterol will not deposit from plasma of low cholesterol content even though the mechanical conditions of stress and strain are favorable. However, the greater the concentration of cholesterol the greater will be the fatty deposition in the arteries subject to the greatest strain. Aschoff emphasizes that the lipoid content of the plasma is not the primary cause of atheroma but it determines the degree of fatty infiltration in a previously produced hyaline ground substance. This contention is supported by observations made before and during World War I. Before the war atheromatosis was frequently observed in normal young individuals; with a lessening of the food supply during the war the atheromata decreased.

That hypercholesterolemia may produce atherosclerosis experimentally has been recognized since 1908 when Anitschkow produced this lesion in rabbits by the administration of large amounts of cholesterol. He claimed that it represented the counterpart of

arteriosclerosis in man (37). Leary (90) concurs in this view. He considers coronary sclerosis as a part of a generalized metabolic disease associated with cholesterol deposits in the subendothelial layers of the arteries in individuals with a hereditary weak cholesterol metabolism consuming a diet of high cholesterol content.

There are, however, several differences between experimental and clinical atherosclerosis. For the production of experimental atherosclerosis, there must be large amounts of cholesterol in the diet; the hypercholesterolemia must be marked; the deposit observed in the arteries, moreover, is a part of a general systemic infiltration of lipids in the tissues. The hypercholesterolemia always precedes the deposition of cholesterol but no definite relation has been established between the height and duration of the hypercholesterolemia and the degree of the atherosclerosis.

Duff (43, 44) points out that in experimental atherosclerosis in addition to the hypercholesterolemia there are local alterations in the walls of the arteries which precede the precipitation of lipoids. He feels that these preliminary changes, which have been minimized by most investigators, are due to some injury attendant on the experimental procedure of cholesterol feeding. It has been suggested by Hueper (70) that the arterial walls are injured by colloidal plasmatic disturbances of the lipoids which lower the stability of the cholesterol in solution by changes in the amount or quality of that substance. This colloidal plasmatic instability results in the formation of films and precipitates on the intima, thereby interfering with the nutrition of the vessel wall.

It has been shown experimentally that the administration of thyroid substances and organic and inorganic iodides prevents arterial deposition of cholesterol (171). With the administration of thyroid blood cholesterol concentration is reduced. Therefore the protective effect of thyroid gland preparations is probably related to an increased ability to dispose of excessive amounts of cholesterol introduced in the diet. Many hypotheses have been put forward to explain the prophylactic effect of the iodides. Turner and Khayat (172) demonstrated that the ability of the iodides to prevent atheromatous changes in the rabbits' arteries depends upon the thyroid gland; the iodine is ineffective in the absence of the thyroid. Since ingestion of cholesterol, dissolved in oil, produces hyperlipemia and deposits in the aorta, it seemed logical to suppose that the iodides prevented the lipemia. Page and Bernhard (123), however, have shown that administration of organic iodides to rabbits fed cholesterol in olive oil did prevent the production of atherosclerosis, but caused the development of a persistent lipemia which was more marked than that produced in rabbits fed cholesterol but no iodine. These findings support the theory that the deposition of lipids depends upon tissue factors. Page and Bernhard suggest that this variable would offer at least a partial explanation of localized atherosclerotic plaques and that atherosclerosis is not a generalized disease. It cannot be inferred from this, according to

Duff (43) that the thyroid plays a part in the etiology of human arteriosclerosis since the etiology of hypercholesterolemia in human arteriosclerosis is doubtful. On the basis of the experimental findings there are, moreover, no evidences that the administration of iodides would be of value in the prevention or treatment of this disease.

If hypercholesterolemia were the determining factor in human atherosclerosis a relationship closer than has been demonstrated should exist between the blood lipids and the disease. From the review of Hirsch and Weinhouse (69) the consensus seems to be that most cases of arteriosclerosis unassociated with diabetes and hypothyroidism do not show hypercholesterolemia, and that the disease may develop without demonstrable hyperlipemia. They conclude that although hyperlipemia, and especially an excess of cholesterol, may favor the development of atherosclerosis and a greater deposition of lipids in the vessel wall, factors in the tissue are concerned with the actual lipid deposition since lipid deposits do not occur in normal arteries even with hypercholesterolemia.

This conception has been emphasized by Klotz (87) who demonstrated the greater affinity of the injured vessel wall, as shown by hyaline degeneration, for fatty materials. The concept of a local primary injury to the vessel wall in human arteriosclerosis and the causative mechanism has been discussed recently by Hueper (70). In his opinion there is a fundamental mechanism common to all agents, namely the impairment of the nutrition and oxygenation of the arterial wall. There are many agents which cause hypotonic and hypertonic changes in the vessel wall, hypotensive and hypertensive intravascular hydrostatic changes, and hematic anoxemia. Colloidal plasmatic disturbances due to disturbance of lipoids, carbohydrates, and proteins also produce injury of the vessel wall but atheroma and atherosclerosis are produced only by disturbances in the lipid and carbohydrate metabolism, both of which are common to the diabetic individual. This had been suggested previously by Rabinowich (132) who found that the colloidal osmotic pressure in diabetic patients with hypercholesterolemia was greater than normal. He also raised the question whether a long-continued increase in colloidal osmotic pressure is responsible for the marked incidence of cardiovascular disease in diabetics. The development of acidosis, ketogenic or from the ash content of the diet, with dehydration, may also tend to cause injury to the intima. In the diabetic individual the disturbed carbohydrate metabolism with fluctuations in the blood sugar concentration is another factor which may prove to be of paramount importance.

Other theories have been suggested to explain the high incidence of arteriosclerosis in diabetics. Rabinowich (133) points out that since cholesterol is abundant in both blood and tissues of the diabetic it is reasonable to suppose that allied substances such as ergosterol are also present in increased amounts. It is possible, therefore, that because of exposure of the skin to sunlight, the tissues of the diabetic are being bombarded constantly with irradiated ergosterol and

this are exposed to calcification. Opposed to this is the wide range of vitamin D between the dose which is therapeutic and that which is capable of producing arteriosclerotic changes in the vessels. Dragstedt and associates (42), from experimental work on depauperated dogs, observed accumulations of fat in the liver due to deficiency of the pancreatic hormone, lipocaine. They thought that the latter substance might possibly play a role in presevenile arteriosclerosis of diabetes mellitus.

It would seem that injury to the intima of the artery from hyperglycemia, acidosis, and disturbed colloidal osmotic pressure, coupled with the tendency of the diabetic individual to have high blood lipids, furnishes a logical explanation for the prevalence of atherosclerosis in this disease. The primary arterial injury is probably the initial event (43) and the one abnormal factor responsible for the subsequent train of events. Hypercholesterolemia may not be essential for the deposition of lipoids in the vessel wall since the normal blood cholesterol concentration is near the point of saturation. Hyperlipemia may influence the amount of deposition of cholesterol in the arteries, but hypercholesterolemia alone is probably not the causative factor. This may be inferred from the observations of Blackman (13) who found at postmortem examination that children with lipoid nephrosis and more or less constant hypercholesterolemia did not show any alterations in their arteries which might not be found in children of the same age who died from other diseases.

If hyperlipemia and tissue changes of the arterial wall which increase their susceptibility to plasma lipids are the causes of abnormal precipitation of cholesterol and other lipids in the intimal coat of the vessel, the elimination of these factors is the first step in the prevention of premature atherosclerosis.

Joslin (84) has raised the question of the possibility that the high fat and high cholesterol diet formerly prescribed is a factor in the prevalence of arteriosclerosis, since the foundation is laid years before it becomes clinically manifest. Considerable literature has accumulated with regard to the fat in the diet in diabetes mellitus. Page (122), reviewing the effect of dietary fat in this disease, comes to the conclusion that although fat normally increases in the blood after meals, the post-absorptive level in diabetics who metabolize adequate amounts of carbohydrates is not affected appreciably by a diet high in fat.

Since the fat in the blood of the individual is related to the quantity of carbohydrate being oxidized, it seems reasonable to expect a lowering of the cholesterol concentration with diets high in carbohydrates, whether or not insulin is used to oxidize the carbohydrates. Rabinowitch (135) found that the effect of high carbohydrate-low caloric diet on the blood cholesterol is an immediate and sustained decrease in plasma cholesterol. In a series of comparable cases, the average reduction of cholesterol was 128 mg. per cent with the high carbohydrate-low caloric diet, whereas with the older diets the average reduction was only 14 mg. per cent.

After instituting a high carbohydrate-low caloric diet, Rabinowitch (135) observed that xanthosis and gangrene, conditions commonly associated with hypercholesterolemia and cardiovascular disease, largely disappeared. In a study of a series of individuals 50 years of age or under who had had diabetes for 5 years or more, he found (134) an incidence of vascular disease of 85.2 per cent; with the high carbohydrate-low caloric diet the incidence was about 28 per cent. In his opinion the excess cholesterol appeared to be an influencing factor although the duration of the diabetes could not be entirely excluded. Geyelin (56) in a study of the treatment of diabetes mellitus over a 10-year period, found that one of the most striking features of the change from the low to the high carbohydrate diet was the invariability with which a pre-existing hypercholesterolemia could be reduced to normal blood cholesterol levels. With various types of diets, except those high in carbohydrates, and especially when the fat constitutes more than 50 per cent of the calories, there are always a few patients who show hypercholesterolemia for years. This occurs even if the diabetes is under apparently perfect control with the absence of glycosuria, ketonuria, and hyperglycemia. A change to the high carbohydrate diet with a ratio of carbohydrate-fat in grams of 3:1 or preferably 4:1 will overcome such persistent hypercholesterolemia in a few weeks. Joslin (83) maintains that the methods of controlling the blood cholesterol concentration in diabetes are indefinite. He points out that, if overnutrition is avoided, it is not necessary that the fat in a low caloric diet be low and the carbohydrate high in order to obtain a lowering of the blood cholesterol concentration. He claims that in individual cases even diets including large amounts of cholesterol-rich food such as eggs do not raise the blood cholesterol concentration appreciably above normal. Rabinowitch (131) also favors under-nutrition and he advocates a high carbohydrate-low fat diet because this method of treatment tends to keep the cholesterol concentration within normal limits more easily than other diets. Whether the lowering of cholesterol is due to undernutrition or the high carbohydrate-low fat diet is controversial. Obesity in diabetes is, however, undesirable, for in 1000 diabetics studied by Joslin (85) an increase of body fat preceded the onset of diabetes in 77 per cent.

The reduction of plasma cholesterol concentration in diabetes since the introduction of insulin probably is due to the improved control of the diabetes rather than to the fat content in the diet as such. Treatment of hypercholesterolemia in this disease thus would consist of the treatment of the diabetes.

The factor or factors causing injury to the vessel wall usually are minimized in any discussion of atherosclerosis in the diabetic individual. The disturbance of the colloidal osmotic balance due to disorders of the carbohydrate metabolism may be just as important, or more so, in initiating the primary injury to the vessel wall. Since the introduction of insulin there has been a definite decrease in the intensity of the dam-

age which is the result of long exposure to diabetes. With the better control of diabetes not only hypercholesterolemia but factors which increase the susceptibility of the tissues in the arterial wall such as acidosis and hyperglycemia are minimized or eliminated. It must be borne in mind, as Rabinowitch has pointed out, that it is not the insulin per se, but the control of the disease, which protects the individual from premature arteriosclerosis. Time will show whether pre-

senile atherosclerosis can be prevented by the long-continued application of adequate treatment in diabetes. If the presumption is correct that both hypercholesterolemia and tissue injury can be prevented by adequate treatment of the disease, the outlook for the diabetic, especially the young individual, has become much more favorable. Complications such as arteriosclerosis will then occur only in the inadequately treated or neglected patient.

REFERENCES

1. Adler, A., and H. Lemmel. Zur feineren Diagnostik der Leberkrankheiten. I. Cholesterin und Cholesterin-Ester im Blute Leberkranker. Deutsches Arch. f. klin. Med., 158: 173-213, Jan. 1928.
2. Andrews, E., L. E. Dostal, M. Goff and L. Hrdina. The mechanism of cholesterol gallstone formation. Ann. Surg., 96: 615-622, 1932.
3. Andrews, E., L. Hrdina and L. E. Dostal. Etiology of gallstones. II Analysis of duet bile from diseased livers. Arch. Surg., 25: 1081-1089, Dec. 1932.
4. Andrews, E., R. Schoenheimer and L. Hrdina. Etiology of gallstones. I Chemical factors and the role of the gallbladder. Arch. Surg., 25: 796-810, October 1932.
5. Arndt, H. J. Zur Kenntnis des Cholesterinstoffwechsels. Ztschr. f. d. ges. exp. Med., 54: 391-414, 1927.
6. Aron, M. Le titrage des hormones préhypophysaires dans l'urine humaine; son intérêt dans l'exploration fonctionnelle des diverses glandes endocrines. Bull. Acad. de Med., Paris, 111: 273-275, Feb. 20, 1934.
7. Aschoff, L. Lectures on Pathology. Paul B. Hoeber, New York, 1924. Pp. 206-232.
8. Aschoff, L. Zur Frage der Cholesterinbildung in der Gallenblase. Münchener med. Wochenschr., 53: 1847-1848, Sept. 18, 1906.
9. Barreda, P. Über den diagnostischen Wert von Blutcholesterinbestimmungen nach peroraler Cholesterinbelastung. Klin. Wochenschr., 13: 290-292, Feb. 24, 1934.
10. Bartels, E. C. Liver function in hyperthyroidism as determined by the hippuric acid test. Ann. Int. Med., 12: 652-674, Nov. 1938.
11. Bashour, J. T., and L. Bauman. The solubility of cholesterol in bile salt solutions. J. Biol. Chem., 121: 1-3, Oct. 1937.
12. Beumer, H., and F. Hepner. Über die Ausscheidungswege des Cholesterins. Ztschr. f. d. ges. exp. Med., 64: 787-797, 1929.
13. Blackman, S. S. Pneumocoecal lipoid nephrosis and the relation between nephrosis and nephritis. I. Clinical and anatomical studies. Bull. Johns Hopkins Hosp., 55: 1-56, 1934.
14. Bloor, W. R. Role of fat in the diet. J. A. M. A., 119: 1018-1025, July 25, 1942.
15. Blottner, H. Blood fat tolerance tests in malnutrition and obesity. Arch. Int. Med., 55: 121-130, Jan. 1935.
16. Blumgart, H. L., and D. Davis. Hypothyroidism induced by complete removal of normal thyroid gland in treatment of chronic heart disease. Endocrinology, 18: 693-700, 1934.
17. Bodansky, M. and O. Bodansky. Biochemistry of disease. New York, The MacMillan Company, 1940, p. 71.
18. Boothby, W. M., J. Berkson and W. A. Plummer. The variability of the basal metabolism: Some observations concerning its application in conditions of health and disease. Ann. Int. Med., 11: 1014-1023, Dec. 1937.
19. Boothby, W. M., I. Sandiford, K. Sandiford and J. Slosse. The effect of thyroxin on the respiratory and nitrogenous metabolism of normal and myxedematous subjects. Trans. Assoc. Am. Phys., 40: 195-228, 1925.
20. Boyd, E. M. The lipemia of pregnancy. J. Clin. Investigation, 13: 347-363, March 1938.
21. Boyd, E. M. Diurnal variations in plasma lipids. J. Biol. Chem., 110: 61-70, June 1935.
22. Boyd, E. M. Blood lipids in the puerperium. Am. J. Obst. & Gynec., 29: 797-805, 1935.
23. Boyd, E. M., and W. F. Connell. Thyroid disease and blood lipids. Quart. J. Med., 5: 455-460, Oct. 1936.
24. Boyd, E. M., and W. F. Connell. The lipopenia of hyperthyroidism. Quart. J. Med., 6: 231-239, July 1937.
25. Boyd, E. M., and W. F. Connell. Plasma lipids in the diagnosis of mild hypothyroidism. Quart. J. Med., 6: 467-471, Oct. 1937.
26. Boyd, E. M., and W. F. Connell. Lipopenia associated with cholesterol Estersturz in parenchymatous hepatic disease. Arch. Int. Med., 61: 755-761, May 1938.
27. Boyd, E. M., W. F. Connell, and A. M. Doyle. Plasma lipids in anxiety states and their comparison with the lipopenia of hyperthyroidism. Quart. J. Med., N. S., 8: 47-50, Jan. 1939.
28. Boyd, W. Studies in gallbladder pathology. Brit. J. Surg., 10: 337-356, Jan. 1923.
29. Bronstein, I. P. Studies in cretinism and hypothyroidism in childhood. I. Blood cholesterol. J. A. M. A., 100: 1661-1663, May 27, 1933.
30. Brueh, H. Obesity in children. II. Basal metabolism and serum cholesterol of obese children. Am. J. Dis. Child., 58: 1001-1022, Nov. 1939.
31. Bruger, M., and H. O. Mosenthal. The immediate response of the plasma cholesterol to the injection of insulin and of epinephrine in human subjects. J. Clin. Investigation, 13: 399-409, May 1934.
32. Bürger, M. Der Cholesterinhalt beim Menschen. Ergebni. d. inn. Med. u. Kinderh., 34: 583-701, 1928.
33. Campbell, J. M. H. Cholesterol in the blood in cases of gallstones. Quart. J. Med., 18: 123-131, Oct. 1924.
34. Campbell, J. M. H. Critical review: Cholesterol in health and disease. Quart. J. Med., 18: 393-422, July 1925.
35. Carter, R. F., C. H. Green, J. R. Twiss and R. Hotz. Etiology of gallstones. A critical survey of the literature and a study of the applicability of various theories in two hundred and thirty-nine operative cases. Arch. Surg., 39: 691-710, Nov. 1939.
36. Castex, M. R., and M. Seltingerart. La colesterinemia y la calcemia en los estados tiroideos; sus relaciones con el metabolismo basal. Rev. Soc. de Med. Int., 1: 514-525, 1925.
37. Cowdry, E. V. Arteriosclerosis: A survey of the problem. New York, MacMillan Company, 1933.
38. Cutting, W. C., D. A. Ryland and M. L. Tainter. Relationship between blood cholesterol and increased metabolism from dinitrophenol and thyroid. J. Clin. Investigation, 13: 547-552, July 1934.
39. Dostal, L. E., and E. Andrews. Etiology of gallstones. III. The effect of diet on the bile salt-cholesterol ratio. Arch. Surg., 26: 258-271, Feb. 1933.
40. Dostal, L. E., L. Hrdina and M. Goff. Is Cholesterol excreted by the gallbladder mucosa? Proc. Soc. Exper. Biol. & Med., 29: 541-542, Feb. 1932.
41. Doubilet, H., and R. Colp. Total bile acid-cholesterol ratio in human and in canine bile. Arch. Surg., 36: 998-1018, June 1938.

42. Dragstedt, L. R., D. E. Clark, O. C. Julian, C. Vermeulen and W. C. Goodpasture. Arteriosclerosis in pancreatic diabetes. *Surgery*, 8: 353-361, 1940.
43. Duff, G. L. Experimental cholesterol arteriosclerosis and its relationship to human arteriosclerosis. *Arch. Path.*, 20: 81-123, 259-304, July & Aug. 1935.
44. Duff, G. L. The nature of experimental cholesterol arteriosclerosis in the rabbit. *Arch. Path.*, 22: 161-182, Aug. 1936.
45. Eitel, H. and A. Loeser. Schilddrüsentätigkeit und Hypophysenvorderlappen. *Klin. Wochenschr.*, 11: 1748-1751, Oct. 15, 1932.
46. Elman, R., and E. A. Graham. The pathogenesis of the "strawberry" gallbladder (Cholesterosis of the gallbladder). *Arch. Surg.*, 24: 14-22, Jan. 1932.
47. Epstein, A. A., and H. Lande. Studies on blood lipoids. I. The relation of cholesterol and protein deficiency to basal metabolism. *Arch. Int. Med.*, 30: 563-577, Nov. 1922.
48. Epstein, E. Z. Cholesterol metabolism and liver disorders. *Rev. Gastroenterology*, 4: 12-19, March 1937.
49. Feigl, J. Über das Vorkommen und die Verteilung von Fetten und Lipoiden im Menschlichen Blutplasma bei Ikterus und Cholämie. *Chemische Beiträge zur Kenntnis spezifischer Lipämien*. *Biochem. Ztschr.*, 90: 1-38, 1918.
50. Fowweather, F. S., and G. A. Collinson. Certain chemical changes associated with gallstones with special reference to the relation between gallstones and hypercholesterolemia. *Brit. J. Surg.*, 14: 583-606, April 1927.
51. Fox, F. W. The composition of human bile and its bearing upon sterol metabolism. *Quart. J. Med.*, 21: 107-120, Oct. 1927.
52. Gardner, J. A., and H. Gainsborough. Studies on the cholesterol content of normal human plasma. III. On the so-called alimentary hypercholesterolemia. *Biochem. J.*, 22: 1048-1056, 1928.
53. Gardner, J. A., and H. Gainsborough. Studies on the cholesterol content of normal human plasma. Biochem. J., 21: 130-140, 1927.
54. Gardner, J. A., and H. Gainsborough. The relationship of plasma cholesterol and basal metabolism. *Brit. M. J.*, 2: 935-937, Nov. 24, 1928.
55. Gardner, J. A., and H. Gainsborough. Blood cholesterol studies in biliary and hepatic disease. *Quart. J. Med.*, 23: 465-483, July 1930.
56. Geyelin, H. R. The treatment of diabetes with insulin (after ten years). *J. A. M. A.*, 104: 1203-1208, April 6, 1935.
57. Gibbs, C. B. F., E. Buckner and W. R. Bloor. The cholesterol to cholesterol ester ratio in the plasma of diabetics with advanced arteriosclerosis. *New England J. Med.*, 209: 384-386, Aug. 24, 1933.
58. Gildea, E. F., E. Kahn and E. B. Mai. The relationship between body build and serum lipoids and a discussion of these qualities as pyknophilic and leptophilic factors in the structure of the personality. *Am. J. Psychiat.*, 92: 1247-1260, May 1936.
59. Gildea, E. F., E. B. Mai and J. P. Peters. Serum lipoids and protein in hypothyroidism. *J. Clin. Investigation*, 18: 739-755, Nov. 1939.
60. Gildea, E. F., E. B. Mai and R. W. Biach. Serum protein, nitrogen and lipoids in schizo-phrenic and manic-depressive psychoses. *Arch. Neurol. & Psychiat.*, 43: 932-947, May 1940.
61. Gilligan, D. R., M. C. Volk, D. Davis, and H. L. Blumgart. Therapeutic effect of total ablation of normal thyroid on congestive heart failure and angina pectoris. *Arch. Int. Med.*, 54: 746-757, Nov. 1934.
62. Goodkind, R. P., and H. L. Higgins. Hypothyroidism in infants and children with reference to ultimate prognosis concerning intelligence and to withdrawal of thyroid therapy as diagnostic measure. *New England J. Med.*, 224: 722-726, April 21, 1941.
63. Gongh, N. Effect of diet on the concentration of cholesterol in blood and bile. *Brit. M. J.*, 2: 390-391, Sept. 25, 1943.
64. Greene, C. H., R. Hotz, and E. Leahy. Clinical value of determination of cholesterol esters of blood in hepatic disease. *Arch. Int. Med.*, 65: 1130-1143, June 1930.
65. Gross, D. M. B. A statistical study of cholelithiasis. *J. Path. & Bact.*, 32: 503-526, July 1929.
66. Havers, K. Experimentelle Untersuchungen über Physiologie und Pathologie des Cholesterinstoffwechsel mit besonderer Berücksichtigung der Schwangerschaft. *Deutsches Arch. f. klin. Med.*, 115: 267-289, June 5, 1914.
67. Hess, J. H. Blood cholesterol and creatine excretion in the urine as aids to diagnosis and treatment of hypothyroidism. *Ann. Int. Med.*, 8: 607-611, Nov. 1934.
68. Hinton, J. W. The adrenalin test and cholesterol determination in the diagnosis of borderline hyperthyroidism. *Am. J. M. Sc.*, 180: 681-686, 1930.
69. Hirsch, E. F., and S. Weinhouse. The role of the lipids in atherosclerosis. *Physiol. Rev.*, 23: 185-202, July 1943.
70. Hueper, W. C. Arteriosclerosis. *Arch. Path.*, 38: 162-181, Sept. 1944.
71. Hunt, H. M. Cholesterol in blood of diabetics treated at the New England Deaconess Hospital. *New England J. Med.*, 201: 659-667, Oct. 3, 1929.
72. Hunt, H. M., and J. S. DeFrates. The relation of diabetes mellitus and cholelithiasis. *New England J. Med.*, 207: 245-254, Aug. 11, 1932.
73. Hunt, H. M. In Joslin, E. P., H. F. Root, P. White and A. Marble. *The treatment of diabetes mellitus*. 7th ed. Philadelphia, Lea & Febiger, 1940.
74. Hurxthal, L. M. Blood cholesterol in thyroid disease. I. Analysis of findings in toxic and in nontoxic goitre before treatment. *Arch. Int. Med.*, 51: 22-32, Jan. 1933.
75. Hurxthal, L. M. Blood Cholesterol in thyroid disease. *Arch. Int. Med.*, 52: 86-95, July 1933.
76. Hurxthal, L. M. Blood cholesterol and thyroid disease. III. Myxedema and hypercholesterolemia. *Arch. Int. Med.*, 53: 762-781, May 1934.
77. Hurxthal, L. M. Blood cholesterol and hypometabolism, suprarenal and pituitary deficiency, obesity, and miscellaneous conditions. *Arch. Int. Med.*, 53: 825-831, June 1934.
78. Hurxthal, L. M., and H. M. Hunt. Clinical relationship of blood cholesterol with a summary of our present knowledge of cholesterol metabolism. *Ann. Int. Med.*, 9: 717-725, Dec. 1935.
79. Hurxthal, L. M., and H. N. Simpson. Hypothyroidism, Hypercholesterolemia. *J. Clin. Endocrinol.*, 1: 450-452, May 1941.
80. Ivy, A. C. Factors concerned in the evacuation of the gallbladder. *Medicine*, 11: 345-370, Sept. 1932.
81. Ivy, A. C. The applied physiology of bile secretion and bile salt therapy. *J. A. M. A.*, 117: 1151-1154, Oct. 4, 1941.
82. Jenkinson, E. L. Cholecystography. *J. A. M. A.*, 107: 755-757, Sept. 5, 1936.
83. Joslin, E. P. An appraisal of the present treatment of diabetes. *J. A. M. A.*, 97: 595-602, Aug. 29, 1931.
84. Joslin, E. P., H. F. Root, P. White, and A. Marble. *The treatment of diabetes mellitus*, 5th ed., Philadelphia, Lea & Febiger, 1935.
85. Joslin, E. P., H. F. Root, P. White and A. Marble. *The treatment of diabetes mellitus*. 7th ed. Philadelphia, Lea & Febiger, 1940.
86. Judd, E. S., and S. H. Mentzer. Cholesterosis of the gallbladder. *California and West. Med.*, 27: 337-339, Sept. 1927. *Ibid.* 477-489, Oct. 1927.
87. Klotz, O. Fatty degeneration of the intima of arteries. *J. Med. Research*, 32: 27-43, 1915.
88. Laroche, G. Les variations de la cholestérolémie chez les thyroïdiens. *Presse méd.* 1: 268-269, Feb. 27, 1929.
89. Lawrence, R. D. Diabetes: With special reference to high carbohydrate diets. *Brit. M. J.*, 2: 517-521, Sept. 16, 1933.
90. Leary, T. Atherosclerosis, the important form of arteriosclerosis, a metabolic disease. *J. A. M. A.*, 105: 475-481, Aug. 17, 1935.
91. Lehnher, E. R. Arteriosclerosis and diabetes mellitus. *New England J. Med.*, 208: 1307-1313, June 1933.
92. Leopold, J. S., A. Bernhard and A. Tow. Changes of the blood lipid in children. *Am. J. Dis. Child.*, 43: 882-888, April 1932.
93. Levy, B. Les variations du cholestérol chez les bascudoviens, traités par la radiothérapie. *Bull. et mém. Soc. med. d'hôp. de Paris*, 55: 1844-1856, Dec. 4, 1931.
94. Lichtman, S. S. Liver function in hyperthyroidism. *Arch. Int. Med.*, 50: 721-729, Nov. 1932.
95. Luden, G. Studies on cholesterol. IV. Experiments concerning the relation of the diet, the blood cholesterol, and the lymphoid defense. *J. Lab. & Clin. Med.*, 3: 141-172, Dec. 1917.
96. Luden, G. Studies on cholesterol. V. The blood cholesterol in malignant disease and the effect of radium on the blood cholesterol. *Collected Papers of the Mayo Clinic*, 10: 470-487, 1918. Saunders, Philadelphia.
97. Mai, E. B., and E. F. Gildea. Serum lipoids in malnutrition. *J. Clin. Investigation*, 15: 203-214, March 1936.

98. Man, E. B., and E. F. Gildea. Variations in lipemia of normal subjects. *J. Biol. Chem.*, 119: 769-779, July 1937.
99. Man, E. B., E. F. Gildea and J. P. Peters. Serum lipoids and proteins in hyperthyroidism. *J. Clin. Investigation*, 19: 43-59, Jan. 1930.
100. Man, E. B., and J. P. Peters. Lipoids of serum in diabetic acidosis. *J. Clin. Investigation*, 13: 237-261, March 1934.
101. Man, E. B., and J. P. Peters. Serum lipoids in diabetes. *J. Clin. Investigation*, 14: 579-594, Sept. 1935.
102. Mann, F. C. The liver and medical progress. *J. A. M. A.*, 117: 1577-1582, Nov. 1941.
103. Mason, R. L. H. M. Hunt and L. M. Hurxthal. Blood cholesterol values in hyperthyroidism and hypothyroidism. Their significance. *New England J. Med.*, 203: 1273-1278, Dec. 25, 1930.
104. McGee, L. C. Blood cholesterol in disturbances of the basal metabolic rate. *Ann. Int. Med.*, 9: 728-738, Dec. 1935.
105. McMaster, P. D. Studies on the total bile: Influence of diet upon the output of cholesterol in bile. *J. Exper. Med.*, 40: 25-42, July 1924.
106. Mentzer, S. H. Cholesterosis of the gallbladder. *Am. J. Path.*, 1: 383-388, July 1925.
107. Mentzer, S. H. The pathogenesis of biliary calculi. *Arch. Surg.*, 14: 14-28, Jan. 1927.
108. Mentzer, S. H. The status of gallbladder surgery. *J. A. M. A.*, 90: 607-610, Feb. 25, 1928.
109. Mjassnikow, A. L. Beiträge zur Konstitutionsforschung. 2. Blutcholesteringehalt und Konstitution. *Ztschr. f. klin. Med.*, 105: 228-244, 1927.
110. Moynihan, B. Some aspects of cholelithiasis. *Brit. M. J.*, 1: 393-398, Feb. 28, 1925.
111. Muhlböck, O., and C. Kaufmann. Der Cholesteringehalt im Blut und Serum bei gesunden Frauen in den verschiedenen Lebensaltern und seine Beziehungen zur Sexualfunktion. *Ztschr. f. d. ges. exper. Med.*, 102: 461-468, 1938.
112. Müller, G. L. The cholesterol metabolism in health and in anæmia. *Medicine*, 9: 110-174, May 1930.
113. Müller, G. L., and J. H. Talbott. The effect of high altitudes on the cholesterol, lecithin and fatty acids in the plasma of healthy men. *Arch. Int. Med.*, 47: 855-860, June 1931.
114. Musser, J. H. Medical treatment of gallstones and cholecystitis. *Proc. Interst. Postgrad. M. A. North America*, 1947: 33-38, 1942.
115. Newman, C. Physiology of the gallbladder and its functional abnormalities (Goulstonian Lecture). *Lancet*, 1: 785-791, April 15; 896-901, April 29, 1932.
116. Nicholls, E. G., and W. A. Perlzweig. The plasma fats and the iodine absorption capacity of the fatty acids in hyperthyroidism. *J. Clin. Investigation*, 5: 195-204, Feb. 1928.
117. Offenkrantz, F. M. Serum cholesterol fluctuations during the menstrual cycle. *Am. J. Clin. Path.*, 8: 536-546, Sept. 1938.
118. Okey, R. Gallstone formation and intake of B Vitamins in cholesterol-fed guinea pig. *Proc. Soc. Exper. Biol. & Med.*, 51: 349-350, Dec. 1942.
119. Okey, R., and R. E. Boyden. Studies of the metabolism of women. III. Variations in the lipid content of blood in relation to the menstrual cycle. *J. Biol. Chem.*, 72: 261-281, March 1927.
120. Okey, R., and D. Stewart. Diet and blood cholesterol in normal women. *J. Biol. Chem.*, 99: 717-727, Feb. 1933.
121. Oppenheim, E., and Bruger, M. The effect of a high-fat test meal on blood cholesterol in normal and obese individuals. *Am. J. M. Sc.*, 205: 77-82, Jan. 1943.
122. Page, I. H. Some aspects of the nature of the chemical changes occurring in atheromatosis. *Ann. Int. Med.*, 14: 1741-1755, April 1941.
123. Page, I. H., and W. G. Bernhard. Cholesterol-induced atherosclerosis. Its prevention in rabbits by the feeding of an organic iodine compound. *Arch. Path.*, 19: 530-536, April 1935.
124. Page, I. H., E. Kirk, W. H. Lewis, W. R. Thompson and D. D. Van Slyke. Plasma lipids of normal men at different ages. *J. Biol. Chem.*, 111: 613-639, Nov. 1935.
125. Parhon, C. I., and I. Ornstein. Influence of Thyroxin on Cholesterol and Lipaemia. *Compt. Rend. Soc. de Biol.*, 108: 303-304, May 9, 1931.
126. Phenister, D. B., H. G. Aronsohn and R. Pepinlay. Variation in the cholesterol, bile pigment and calcium salts contents of gallstones formed in gallbladder and in bile duets with the degree of associated obstruction. *Ann. Surg.*, 109: 161-186, Feb. 1939.
127. Pickens, M., G. O. Spanner and L. Bauman. The composition of gallstones and their solubility in dog bile. *J. Biol. Chem.*, 95: 505-507, March 1932.
128. Pickhardt, O. C., A. Bernhard, and I. L. Kohn. The significance of the cholesterol partition of the blood serum in surgery of the gallbladder. *Ann. Int. Med.*, 110: 701-722, 1939.
129. Rabinowitch, I. M. The cholesterol content of blood plasma in diabetes mellitus. *Arch. Int. Med.*, 43: 363-371, March 1929.
130. Rabinowitch, I. M. The cholesterol content of blood plasma in juvenile diabetes. *Arch. Int. Med.*, 43: 372-375, March 1929.
131. Rabinowitch, I. M. Experience with a high carbohydrate-low calorie diet for the treatment of diabetes mellitus. *Canad. M. A. J.*, 23: 489-498, Oct. 1930.
132. Rabinowitch, I. M. Diabetes Mellitus. The colloidal osmotic pressure of the blood. *Arch. Int. Med.*, 46: 752-767, Nov. 1930.
133. Rabinowitch, I. M. Observation on the significance of the cholesterol content of the blood plasma in diabetes mellitus. *Canad. M. A. J.*, 28: 162-168, Feb. 1933.
134. Rabinowitch, I. M., W. L. Ritchie, and S. H. McKee. A statistical evaluation of different methods for the detection of arteriosclerosis in diabetes mellitus. *Ann. Int. Med.*, 7: 1478-1490, June 1934.
135. Rabinowitch, I. M. Arteriosclerosis in diabetes. I. Relationship between plasma cholesterol and arteriosclerosis. II. Effects of the high carbohydrate-low calorie diet. *Ann. Int. Med.*, 8: 1436-1474, May 1935.
136. Randall, L. O. The effects of insulin on serum lipids and choline esterase in schizophrenia. *J. Lab. & Clin. Med.*, 25: 1025-1028, July 1940.
137. Ravidin, I. S., C. G. Johnston, J. H. Austin and C. Riegel. Studies of gallbladder function: IV. Absorption of chloride from bile-free gallbladder. *Am. J. Physiol.*, 99: 638-647, Feb. 1932.
138. Ravidin, I. S., E. Thorogood, C. Riegel, R. Peters and J. E. Rhoads. The prevention of liver damage. *J. A. M. A.*, 121: 322-325, Jan. 30, 1943.
139. Riegel, C., I. S. Ravidin and C. G. Johnston. Studies of gallbladder function. VI. The absorption of bile salts and cholesterol from the bile-free gallbladder. *Am. J. Physiol.*, 99: 650-665, Feb. 1932.
140. Riegel, C., I. S. Ravidin, P. J. Morrison and M. J. Potter. Studies of gallbladder function. XI. The composition of the gallbladder bile in pregnancy. *J. A. M. A.*, 105: 1343-1344, Oct. 26, 1935.
141. Rony, H. R., and A. J. Levy. Studies on fat metabolism: I. Fat tolerance in obesity. A preliminary study. *J. Lab. & Clin. Med.*, 15: 221-228, 1929.
142. Root, H. F., E. F. Bland, W. H. Gordon and P. D. White. Coronary atherosclerosis in diabetes mellitus. *J. A. M. A.*, 113: 27-30, July 1, 1939.
143. Rothschild, M. A. Zur Physiologie des Cholesterinstoffwechsels: V. Der Cholesteringehalt des Blutes und einiger Organe im Hungerzustand. *Beitr. z. path. Anat. u. z. allg. Path.*, 60: 227-231, 1915.
144. Rous, P., and P. D. McMaster. The concentrating activity of the gallbladder. *J. Exper. Med.*, 34: 47-73, July 1921.
145. Rous, P., P. D. McMaster and D. R. Drury. Observations on some causes of gallstone formation. I. Experimental cholelithiasis in the absence of stasis, infection and gallbladder influences. *J. Exper. Med.*, 39: 77-96, Jan. 1924.
146. Rowe, A. W. Endocrine Studies: XLIII. The gaseous metabolism of some dwarfs and giants. *J. Nutrition*, 7: 573-590, June 1934.
147. Salter, W. T., J. Lerman and J. H. Means. The calorogenic action of thyroxin polypeptide. *J. Clin. Investigation*, 12: 327-334, March 1933.
148. Schally, A. O. Störung und Regulation des Cholesterinstoffwechsels. II. Schilddrüse und Cholesterinstoffwechsel. *Ztschr. f. klin. Med.*, 128: 376-385, 1935.
149. Schittenhelm, A., and B. Eisler. Untersuchungen der Wirkung des thyreotropen Hormons auf die Tätigkeit der Schilddrüse. *Klin. Wochenschr.*, 11: 1002-1008, June 25, 1932.
150. Schönheimer, R. and H. von Behring. Über die Exkretion gesättigter Sterine. *Ztschr. f. physiol. Chem.*, 192: 102-111, 1930.
151. Schube, P. G. Variations in the blood cholesterol of

- man over a time period. *J. Lab. & Clin. Med.*, 22: 280-284, 1936.
152. Seowen, E. F. Thyrotropic hormone of the anterior pituitary in man. *Lancet*, 233: 799-802, Oct. 1937.
153. Shephardson, H. C. Arteriosclerosis in young diabetic patients. *Arch. Int. Med.*, 45: 674-689, May 1930.
154. Shope, R. E. Sugar and cholesterol in the blood serum as related to fasting. *J. Biol. Chem.*, 75: 101-113, Oct. 1927.
155. Slemmons, J. M., and H. J. Stander. The lipoids of maternal and fetal blood at the conclusion of labor. *Johns Hopkins Hosp. Bull.*, 34: 7-10, Jan. 1923.
156. Smith, R. M., and A. Marble. The colorimetric determination of free and combined cholesterol. *J. Biol. Chem.*, 117: 673-684, Feb. 1937.
157. Smyth, F. S., and G. H. Whipple. Bile salt metabolism. I. Influence of chloroform and phosphorus on bile fistula dogs. *J. Biol. Chem.*, 59: 623-636, 1924.
158. Sosman, M. C., L. R. Whitaker, and P. J. Edson. Clinical and experimental cholecystography. *Am. J. Roentgenol.*, 14: 495-503, 1925.
159. Sperry, W. M. Lipid excretion. IV. A study of the relationship of the bile to the fecal lipids with special reference to certain problems of sterol metabolism. *J. Biol. Chem.*, 71: 351-378, Jan. 1927.
160. Sperry, W. M. Cholesterol of the blood plasma in the neonatal period. *Am. J. Dis. Child.*, 51: 84-90, Jan. 1936.
161. Sperry, W. M. The relationship between total and free cholesterol in human blood serum. *J. Biol. Chem.*, 114: 125-133, May 1936.
162. Sperry, W. M. The concentration of total cholesterol in the blood serum. *J. Biol. Chem.*, 117: 391-395, Jan. 1937.
163. Starr, P. Clinical studies with the thyrotropic pituitary hormone. *Proc. Soc. Exper. Biol. & Med.*, 33: 462-464, 1935-1936.
164. Steiner, A., and B. Domanski. Dietary Hypercholesterolemia. *Am. J. M. Sc.*, 201: 820-824, June 1941.
165. Talbot, F. B. Basal metabolism standards for children. *Am. J. Dis. Child.*, 55: 455-459, March 1938.
166. Thannhauser, S. J., and H. Magendantz. The different clinical groups of xanthomatous diseases; a clinical physiological study of 22 cases. *Ann. Int. Med.*, 11: 1662-1746, March 1938.
167. Thannhauser, S. J., and H. M. Schaber. Ueber die Beziehungen des gleichgewichts Cholesterin und Cholesterinester im Blut und Serum zur Leberfunktion. *Klin. Wchnschr.*, 5: 252-253, Feb. 12, 1926.
168. Thompson, W. O., S. G. Taylor, P. K. Thompson, S. B. Nadler and L. F. N. Dickie. The calorigenic action of extracts of the anterior lobe of the pituitary in man. *Endocrinology*, 20: 55-63, Jan. 1936.
169. Thompson, W. O., P. K. Thompson, A. G. Brailey and A. C. Cohen. The calorigenetic action of thyroxin at different levels of basal metabolism in myxedema. *J. Clin. Investigation*, 7: 437-463, Aug. 1929.
170. Topper, A., and H. Muller. Basal metabolism of children of abnormal body weight. *J. A. M. A.*, 92: 1903-1907, June 8, 1929.
171. Turner, K. B. Studies on the prevention of cholesterol atherosclerosis in rabbits. I. The effects of whole thyroid and of potassium iodide. *J. Exper. Med.*, 58: 115-125, July 1933.
172. Turner, K. B. and G. B. Khayat. Studies on the prevention of cholesterol atherosclerosis in rabbits. II. The influence of thyroideectomy upon the protective action of potassium iodide. *J. Exper. Med.*, 58: 127-135, July 1933.
173. Turner, K. B., and A. Steiner. A long term study of the variation of serum cholesterol in man. *J. Clin. Investigation*, 18: 45-59, Jan. 1939.
174. Twiss, J. R., and J. H. Barnard. Disease of biliary tract associated with disturbances in cholesterol metabolism. *J. A. M. A.*, 111: 990-994, Sept. 1938.
175. Von Babarezy, M. Die Bedeutung der Cholesterins in der diätetik der Cholecystopathien. *Ztschr. f. klin. Med.*, 133: 656-664, 1938.
176. Wachstein, M. Über Zwei mit thyreotropem Hormon behandelte Fälle von Myxödem. *Klin. Wchnschr.*, 13: 1434-1436, Oct. 6, 1934.
177. Wade, P. A. Clinical and experimental studies on calcium and cholesterol in relation to the thyroid parathyroid apparatus. *Am. J. M. Sc.*, 177: 790-816, June 1929.
178. Warren, S. The pathology of diabetes mellitus. 2nd ed. Philadelphia, Lea & Febiger, 1938. Pp. 121-142.
179. Weber, M. R. Das Verhalten einiger biochemischer Blutkomponenten bei operativer Behandlung der Basedow'schen Krankheit. *Ztschr. f. klin. Med.*, 118: 464-473, 1931.
180. Weinhouse, S. The blood cholesterol. *Arch. Path.*, 35: 438-500, March 1943.
181. Weinhouse, S., and E. F. Hirsch. Chemistry of atherosclerosis: I. Lipid and calcium content of the intima and of the media of the aorta with and without atherosclerosis. *Arch. Path.*, 29: 31-41, Jan. 1940.
182. Weller, C. V. Hepatic lesions associated with exophthalmic goitre. *Trans. Assn. Am. Phys.*, 45: 71-76, 1930.
183. Werner, G. Variations de la Cholesterinémie et de l'uremie dans le syndrome athyroïden experimental. *Compt. Rend. Soc. de Biol.*, 100: 928-929, April 8, 1929.
184. Whipple, G. H. The origin and significance of the constituents of the bile. *Physiol. Rev.*, 2: 440-459, July 1922.
185. Whitaker, L. R. The relation of biliary dysfunction to lithiasis. *New York State J. Med.*, 34: 221-236, March 15, 1934.
186. White, P., and H. M. Hunt. Cholesterol of the blood of diabetic children. *New England J. Med.*, 202: 607-616, March 27, 1930.
187. White, F. W., E. Dentsch and S. Maddock. The comparative value of serial hippuric acid excretion, total cholesterol, cholesterol ester and phospho-lipid tests in diseases of the liver. II. A clinical comparison of the tests. *Am. J. Digest. Dis. & Nutrition*, 7: 3-7, 1940.
188. Wilkins, L., W. Fleischmann, and W. Block. Studies on hypothyroidism in childhood: The basal metabolic rate, serum cholesterol and urinary creatinine before treatment. *J. Clin. Endocrinol.*, 1: 3-13, Jan. 1941.
189. Wilkins, L., W. Fleischmann and W. Block. Hypothyroidism in childhood. II. Sensitivity to thyroid medication as measured by the serum cholesterol and the creatine excretion. *J. Clin. Endocrinol.*, 1: 14-23, Jan. 1941.
190. Wilkins, L., and W. Fleischmann. Hypothyroidism in childhood. III. The effect of withdrawal of thyroid therapy upon the serum cholesterol. Relationship of cholesterol, basal metabolic rate, weight, and clinical symptoms. *J. Clin. Endocrinol.*, 1: 91-97, Feb. 1941.
191. Wilkins, L., and W. Fleischmann. Hypothyroidism in childhood. IV. The creatine and cholesterol response to thyrotropic hormone. *J. Clin. Endocrinol.*, 1: 98-108, Feb. 1941.

The Effect of Bile Salts on the Experimental Production of Ulcers in the Dog

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KOELLIKER and Mueller in 1855, were the first to observe that dogs and other animals with biliary fistula frequently develop gastric and duodenal ulcer (1). In 1868 Burkhardt reported that bile and bile acids precipitate pepsin in the acid gastric juice, thereby inactivating it, an effect not reversed by re-acidification to the original pH and, therefore, not merely due to an unfavorable pH, but mainly due to the precipitation of the bile acids by the gastric acid and the simultaneous adsorption of the pepsin on the precipitate (2). This same type of inhibition by bile salts was observed on rennin by Clementi and Pistorio in 1925 (3). Bollman and Mann (1932) found that after ligation of the common duct in dogs 60 per cent of the animals developed ulcers (4). Moreover, Blanck in 1935 showed that in dogs the loss of bile was not only of paramount importance in inducing experimental ulceration, but that by adequate feeding of fresh bile from dogs these changes could be prevented (5). Of 15 dogs with complete drainage of bile, all being supplied with bile by mouth or by a tube entering the upper intestine, duodenal ulcers were observed in two cases by Bachrach et al in 1939 (6).

However, these observations have not been uncontested. As early as 1863 Roehrig noted ecchymoses in the gastrointestinal tract following administration of bile salts (7), and Rywosch (1888) observed the appearance of acute gastric ulcers after oral or par-

enteral introduction of bile salts (8). Tashiro et al (1931) confirmed these findings and reported that the action of bile acids is antagonized by phosphatides, cholesterol oleate and other lipids (9). He believed that substances which produce ulceration of the gastric mucosa in guinea pigs reduce the phosphatide content of the blood and thus remove this protection from the bile salts.

In view of these conflicting reports and the fact that the neutralizing effect of bile upon gastric acidity has been given by most investigators as the explanation of the appearance of ulcers after exclusion of bile, we carried out the following experiments.

Isolated loops of intestines of anesthetized dogs were exposed to acid-pepsin solutions both with and without bile salts as indicated in the first column in Table 1. The pH's of the solutions are listed in the second column. Two groups of experiments were done; in one group the solutions were in contact with the mucosa of the gut under zero cm. pressure and in the other group under a hydrostatic pressure of 90 cm. H₂O. After about 10 or 12 hours, or until a perforated ulcer occurred, the loops were removed and examined grossly and microscopically for damage. Detailed explanations of the technique and method for recording the severity of ulceration have been described elsewhere in this journal (10, 11). The results are given in Table 1.

When the hydrostatic pressure of the solution

TABLE I.—Effect of Bile Salts on Ulcer Formation

Solution	pH	No. Dogs	Zero cm. Pressure			No. Dogs	90 cm. H ₂ O Pressure			
			Time Exposed (minutes)				Time Exposed (minutes)			
			Range	Average	Severity		Range	Average	Severity	
0.1% pepsin* in 0.1N HCl	1.2	15	300-810	700	19	10	60-60	82	4	
0.1% pepsin in 0.1N HCl + 1/2% NaTa** + 1/2% NaG1**	1.25	12	305-825	712	0.4	11	71-238	138	4	
0.1% pepsin in 0.0003N HCl	3.7	10	450-700	600	0	12	330-735	622	0	
0.1% pepsin in 0.01N HCl + 1/2% NaTa + 1/2% NaG1	3.7	6	750-750	750	0	6	300-750	637	0	

* Merck N. F. Powdered.

** Sodium taurocholate and sodium glycocholate, Pfanzlachl, Pure.

From the Department of Physiological Chemistry, University of Alabama, University, Alabama. Submitted April 17, 1945.

was 90 cm. H₂O perforated ulcers occurred in all cases at a low pH favorable for peptic activity. If bile salts were present the time for perforation to appear was 138 minutes as against 82 minutes when the salts were absent. This occurred even though the solutions were at approximately the same pH. At a higher pH, 3.7, the pepsin was inactive whether or not bile salts were present.

The same results, to a lesser degree, were observed when the pressure was zero, the severity of damage being 1.9 without bile salts and 0.4 with the salts.

REFERENCES

1. Koelliker, A. and Mueller, H.: Anlegung von Gallenbl.-fisteln. Verh. Wuerzburger phys. med. Ges., 1855, 5: 213.
2. Burkhardt, R.: Disruption of Gastric Digestion by Bile. Pflueger's Arch. fuer die ges. Physiol., 1868, 1: 208.
3. Clementi, A. and Pistorio, E.: L'azione inhib. della bile sulla coagul. chimosimica del latte. Arch. fisiol., 1925, 23: 473.
4. Bollman, J. L. and Mann, F. C.: Peptic Ulcer in Experimental Jaundice. Arch. Surg., 1932, 24: 126.
5. Blanck, E. E.: Peptic Ulcer—An Experimental Study. Surg. Gyn. and Obs., 1935, 61: 480.
6. Bachrach, W. H., Schmidt, C. R. and Benzell, J. M.: Relation of Bile and Pancreatic Juice to Duodenal Ulcer in Dogs. Proc. Soc. Exp. Biol. and Med., 1939, 40: 322.
7. Roehrig, A.: Einfl. d. Galle auf die Herztaetigkeit. Arch. Heilkunde, 1863, 4: 385.
8. Rywosch, D.: Ueber giftige Wirkung d. Gallensauren. Arbb. Pharm. Inst. Dorpat, 1888, 2:102.
9. Tashiro, Shiro et al: Studies on Bile Salts I-NVIII, Med. Bull. Univ. Cincinnati, 1931, 6:40.
10. Driver, R. L., Chappell, R. H. and Carmichael, E. B.: Effect of Concentration of Pepsin and the Differential Susceptibility of Jejunal Segments in Experimental Jejunal Ulcers in the Dog. Am. Jour. Dig. Dis., 1945, 12: 166.
11. Driver, R. L., Chappell, R. H. and Carmichael, E. B.: Effect of Hydrostatic Pressure on the Experimental Production of Ulcers. Am. Jour. Dig. Dis., 1945, 12: 168.

Hyperinsulinism as a Factor in Peptic Ulcer

by

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IT is indeed fortunate that the simultaneous occurrence of diabetes mellitus and peptic ulcer is so rare for it is very difficult to devise and maintain a diet to take care of both conditions. The former requires the feeding of large amounts of fat and that is precisely what we wish to avoid in the modern handling of diabetes because of the recognized anti-insulinogenic action of fat (1-5). Per contra, a high intake of carbohydrate is of benefit in diabetes because it tends to keep the blood glucose level lower. Although there are many statistical studies that confirm the widely held opinion that the two conditions occur together only rarely (6, 7) Joslin believes that the comparatively low incidence of peptic ulcer in diabetics can be explained by the difference in their age groups (8). He points out that ulcer is a disease of early adult life whereas diabetes usually occurs much later. However, ulcer is a disease of great chronicity and low mortality and we should expect most of such patients to survive to the diabetic age. Furthermore, unless there is some other factor working in opposition, the high fat diets given to ulcer patients should predispose them to the later acquisition of diabetes for such diets have been shown to favor the development of diabetes (9, 10). It can be unequivocally stated that no evidence has ever been offered to show any particularly high incidence of diabetes in treated ulcer patients.

It is generally recognized that ulcers and gall blad-

der disease tend to occur in two distinct constitutional types which differ sharply in many particulars (11). The gall bladder type is very frequently diabetic and, unless all our notions as to constitution and disease are erroneous, we should expect the opposite type to be comparatively free from diabetes. The fact that restriction of fats aids in keeping gall bladder patients freer of symptoms suggests this similarity in type.

No matter what the true explanation, the experience in most diabetic clinics will show that very few of their patients have peptic ulcer. This discussion demonstrates the difficulty in drawing valid conclusions from statistical analysis. The complexity of biological phenomena leads us to make simplifying assumptions in order to reduce the number of variables. Then we can bring the problem within the limited powers of human reasoning—but only far too often we thereby beg the question.

Harris has shown that hyperinsulinism may present the symptoms of peptic ulcer (12). Moderate hypoglycemia can induce hyperperistalsis and spasm which often simulate organic lesions in the stomach and duodenum (13). In fact, there is good reason to believe that these may be the actual precursors of the anatomical change.

Bronchial (allergic) asthma (14, 15) and acute rheumatic fever (16) resemble peptic ulcer in that they, too, are only infrequently found in diabetics. The assumption that these conditions are only rarely as-

SUMMARY

1. Intestinal loops of dogs were exposed to acid-pepsin solutions with and without bile salts at zero and 90 cm. H₂O pressure, and at pH's of approximately 1.2 and 3.7.
2. Bile salts markedly inhibited the digestive action of pepsin on intestinal mucosa at a pH of 1.25.
3. At a pH of 3.7 there was no damage to the mucosa regardless of hydrostatic pressure or the presence of bile salts.

sociated with diabetes because they already have its opposite, hyperinsulinism, led to fruitful investigations. The same assumption may be made with regard to ulcer and this hypothesis is amenable to direct experimental verification. Valid conclusions may be drawn from relatively few cases for a single disagreement will suffice to demolish the theory. Thus we can avoid the pitfalls of reasoning from statistics.

A group of patients with peptic ulcer was subjected to the six hour glucose tolerance test of Harris (17). The patients were selected to meet a few conditions. All had the classical symptoms and signs of peptic ulcer—heartburn and pain related to meals and relieved by alkalies, seasonal variation and abdominal tenderness. None had received any dietary treatment. None had any marked arteriosclerosis for it is conceivable that erosion of a severely sclerotic gastric vessel might mimic true peptic ulcer. Cases with complications, such as melena, hematemesis or perforation were excluded. In each case, the diagnosis of peptic ulcer was as certain as any clinical diagnosis can be but no attempt was made clinically to distinguish between gastric and duodenal ulcer for that differential is notoriously unsatisfactory. Gastric analysis was done in most cases but, as is usually the case, no regularity between the findings and site or size of the lesion could be noted. These findings are not included in this report. The cases can be divided into three groups on the basis of X-ray findings—gastric ulcers, duodenal ulcers and those in which the X-ray failed to demonstrate any anatomical lesion (or at least any large enough to be seen). For the sake of brevity, the results are given in tabular form.

I. GASTRIC ULCER

hrs. after ingesting 100 grams
of glucose.

Case	Fasting	1	2	3	4	5	6	
1	68	162	110	93	88	72*	60	
2	65	127	86	86	82	57*		
3	87	134	100	78	66	63	67	
4	110	138	148	89	57	62	66	
5	78	130	84	75	75	70	52	

II. DUODENAL ULCER

6	66	118	125	80	72	60	55	
7	87	142	69	80	66*			
8	88	136	82	81	82	76	57	
9	88	126	102	99	72	63	58	
10	76	133	74	66	56*			
11	112	142	110	66	58	60	60	
12	108	146	100	76	66*			

III. NO X-RAY FINDINGS

13	66	144	100	72	71	55*		
14	86	124	80	77	76	72	61	
15	84	136	82	70	63	62	53	
16	102	145	98	92	81	66	61	

mgs. glucose per 100 cc. of blood.

* Test had to be stopped because of severe pain.

o Test had to be stopped 20 minutes before the hour because of pain.

In order to avoid the labor and inconvenience of the long test, several patients were given the sixth hour glucose tolerance test (18). Each patient was furnished with a solution containing 100 grams of

glucose with instructions to finish his evening meal by 7 P. M. and to take no other food until the completion of the test. He was awakened at 4 A. M., when he drank the glucose solution and went back to sleep. A single fasting blood glucose determination was made at 10 A. M. Values under 70 mgs. per 100 cc. are considered to be indicative of hyperinsulinism. The results were—62, 69, 69, 70, 62, 59, 66, 67, 49, 65, 57, 60, 60, 55 and 58 mgs. per 100 cc. All determinations were made by the micro Folin-Wu method using capillary blood. The first five of this group had X-ray evidence of gastric ulcer; the rest had their lesions in the duodenum.

These results permit several conclusions to be drawn. We see at once the utter futility of the ordinary fasting blood glucose determination. Blood sugar is so labile that very little information is obtained from its determination after the usual night's fast. The "flatness" of a glucose tolerance curve is only a poor indication of increased sugar tolerance for many of these curves showed very high rises after taking the test dose. However, the uniformly low late values of blood glucose fulfill our prediction that all cases of peptic ulcer would have hyperinsulinism.

There yet remains one important question. Validity of the theory herein offered requires an unforced explanation for the fact that there actually are some cases of peptic ulcer in diabetics. Only three such cases were available for investigation. All happened to have duodenal ulcer. The results with the glucose tolerance test were:

Case	Fasting	1	2	3	4	5	6 hrs.
32	118	186	111	100	75	66	66
33	68	166	222	124	82	72	57
34	160	232	188	162	90	78	61 mgs. per 100 cc.

These curves are typical for what Harris calls "dysinsulinism" (19). The first portion of each is typically diabetic and then there is a drop into the hypoglycemic range. He postulates a time lag in the elaboration of insulin in response to a metabolic demand with a subsequent over production of the hormone. Whether or not this be the true explanation is of no moment. There are some few diabetics who can have spontaneous hypoglycemia and the diabetics with ulcer had curves to indicate this possibility.

All of these patients were treated with Harris' diet for hyperinsulinism (20). This consists of a high fat, low quickly absorbable carbohydrate diet with frequent feedings of rather small meals. Thus we avoid any sudden marked rise in blood sugar which would stimulate the over sensitive islet cells (1, 5). The frequency of feeding prevents any marked postprandial drop in blood glucose. The large amount of fat in the diet is depressant to the insulin apparatus (1, 5, 21). Caffeine is rigorously excluded for that has been found to be a potent exciting cause for hyperinsulinism (17). It induces glycogenolysis, thereby giving a sudden increase in blood glucose which, as far as the insulin apparatus is concerned, is indistinguishable from alimentary hyperglycemia. This diet is quite similar to the modified Sippy diets

so widely used in the ambulatory treatment of peptic ulcer. The patients did very well on it and they did not have to take alkalies for longer than a few weeks. Many of them found that they did not require any powders at all. The diabetic patients were treated just like the others for their diabetes was mild enough to be ignored. Their discomfort was due entirely to the ulcer and they were subjectively much improved. It is interesting that the prohibition of coffee which is part of all ulcer regimens (on purely empirical grounds) is now seen to have a rational basis.

It may be argued that what we call "hyperinsulinism" is not actually due to a surfeit of the hormone. Perhaps we should be content with saying that peptic ulcer is characterized by a tendency toward hypoglycemia. It really makes no difference for, in either case, we find an explanation for the fact that diabetes and ulcer do not occur together very often. However, there is good reason to believe that "hyperinsulinism" is actually due to an increase in circulating insulin. Granted that the glucose tolerance test permits this conclusion only by inference for we cannot readily determine the blood insulin, but cases of islet cell neoplasm in which we cannot seriously doubt the presence of a real excess of insulin behave similarly.

None of these cases had the recognized symptoms of hyperinsulinism—sweating, palpitation, shock, etc. These symptoms are to be found only in marked cases of the disease, where the diagnosis can be made on history alone. But moderate hyperinsulinism may be a fairly common condition revealing its presence only by the results with the long glucose tolerance test.

We have thus demonstrated that peptic ulcer is associated with hyperinsulinism. Although one cannot say that the hyperinsulinism precedes the ulcer or is causally related to it, there is some justification for believing such to be the case. Quite a few cases distinguishable from anatomical peptic ulcers only by the absence of positive X-ray findings had the same type of curves and response to the dietary treatment as those in whom the diagnosis was confirmed on the X-ray plate. Future investigation should clear up this important point.

A bit of speculation seems justified. It has been shown that hyperinsulinism is found in such diversified conditions as ulcer, asthma and acute rheumatic fever. Now all of these conditions are markedly constitutional diseases. The protean nature of hyperinsulinism becomes understandable when we consider the effect of chronic hypoglycemia. Now the normal

blood glucose concentration is not 80 to 120 mgs. per 100 cc. That is the normal *fasting* level and fasting is not physiologic for our hunger leads us to its prompt relief. Normally, the blood glucose probably fluctuates about a mean in the neighborhood of 140 mgs. per 100 cc. In hyperinsulinism, the level is considerably below this and we have, in effect, a state of chronic partial glucose starvation. Since glucose is used to nourish all of the cells of the body their health requires an adequate amount at all times. With inadequate nourishment, we can expect some weak spot to break down after a time. However, we cannot predict just where the break will occur just as we can expect an automobile to get into trouble when we use too lean a fuel mixture but factors beyond our knowledge will determine just which part will fail.

Americans are known to have the largest per capita consumption of coffee in the world. Not content with this excessive use of caffeine, we have added a host of caffeine containing soft drinks to the national dietary. They are drunk in enormous volumes and they may, perhaps, prove to be of significance in the incidence of diseases induced by the excessive use of caffeine. At any rate, we should give the question more thought.

SUMMARY AND CONCLUSIONS

1. Peptic ulcer is found only rarely in diabetics and this suggests some difference in constitution since both are constitutional diseases.
2. Hyperinsulinism can produce the symptoms of peptic ulcer and the chronic hypoglycemia often induces hyperperistalsis and spasm which might lead to ulcer.
3. The assumption that all cases of peptic ulcer have hyperinsulinism furnishes a ready explanation for the diabetic's comparative freedom from the other disease.
4. Experiments showed that peptic ulcer patients actually have hyperinsulinism.
5. The fact that patients with the clinical diagnosis of peptic ulcer but without X-ray confirmation of that diagnosis have the same type of glucose tolerance curves as those in whom the confirmation was present leads to the possibility that the hyperinsulinism, or at least the chronic hypoglycemia, might have some etiological relation to ulcer.
6. The role of caffeine in producing hyperinsulinism suggests that we re-evaluate the assumed harmlessness of that alkaloid.

REFERENCES

1. Sweeney, J. S., Dietary Factors that Influence the Glucose Tolerance Test, *Archit. Med.*, 40: 818, 1927.
2. Rabinowitch, I. M., Experiences with a High Carbohydrate-Low Calorie Diet for the Treatment of Diabetes Mellitus, *Canad. Med. Journ.*, 23: 489, 1930.
3. Rabinowitch, I. M., The Present Status of the High Carbohydrate-Low Calorie Diet for the Treatment of Diabetes, *Canad. Med. Journ.*, 26: 141, 1932.
4. Adlersberg, D., and Porges, O., Die Behandlung Diabetiker mit fetziger Kost, *Klin. Woehenschr.*, 5: 1451, 1926.
5. Himsworth, H. P., The Dietetic Factor Determining the Glucose Tolerance and Sensitivity to Insulin of Healthy Men, *Clinical Science*, 2: 67, 1935.
6. Falta, W., Renaler und Insulärer Diabetes, 378, 1939.
7. Rothenberg, R. E., and Teicher, I., Peptic Ulcer and Diabetes Mellitus, *Am. Journ. Dig. Dis.*, 5: 663, 1938.
8. Joslin, E., Treatment of Diabetes Mellitus, 7th. Ed., 468, 1940.
9. Himsworth, H. P., and Marshall, E. M., The Diet of Diabetes Prior to the Onset of the Disease, *Clinical Science*, 2: 95, 1935.

10. Himsworth, H. P., Diet and Incidence of Diabetes Mellitus, *Clinical Science*, 2: 117, 1935.
11. Stockard, C. R., Constitution and Type in Relation to Disease, *Medicine*, 5: 116, 1926.
12. Harris, S., Gastrointestinal Manifestations of Hyperinsulinism, *Am. Journ. Dig. Dis.*, 2: 557, 1935.
13. Quigley, J. P., Johnson, V., and Solomon, E. I., Action of Insulin on the Motility of the Gastrointestinal Tract, *Am. Journ. Physiol.*, 90: 89, 1929.
14. Abrahamson, E. M., Asthma, Diabetes Mellitus and Hyperinsulinism, *Journ. Clin. Endocrinol.*, 1: 402, 1941.
15. Abrahamson, E. M., A Dietary Treatment for Asthma and Hay Fever, *U. S. Naval Med. Bull.*, 40: 711, 1942.
16. Abrahamson, E. M., Hyperinsulinism as an Etiological Factor in Acute Rheumatic Fever, *Journ. Clin. Endocrinol.*, 4: 71, 1944.
17. Harris, S., The Diagnosis and Treatment of Hyperinsulinism, *Ann. Int. Med.*, 10: 514, 1936.
18. Abrahamson, E. M., A Simplified Test for Hyperinsulinism, *Bull. Reg. Med. Tech.*, 1: 138, 1940.
19. Harris, S., Hyperinsulinism and Dysinsulinism, *J. A. M. A.*, 83: 729, 1924.
20. Harris, S., High Carbohydrate-Low Fat Diets in the Treatment of Diabetes Mellitus and Low Carbohydrate-High Fat Diets in Hyperinsulinism, *The Mississippi Doctor*, 13: 9, 1936.
21. Shepardson, H. C., Glycopenia: The Efficacy of High Fat Diets in the Treatment of Chronic Hypoglycemia, *Endocrinology*, 16: 182, 1932.

Book Reviews

Synopsis of Clinical Laboratory Methods. By W. E. Bray. 3rd Edit., Pp. 528 (\$5.00). St. Louis, C. V. Mosby Co., 1944.

The author and publishers felt the need for a third edition of this laboratory manual because many new procedures have been developed and become well established since publication of the second edition. Included in the present text, in addition to subjects covered previously, are discussions and outlines of the following topics: Hippuric acid liver function test, cholesterol flocculation time, Rh factor and anti-Rh test, determinations of blood levels of salicylates, Koppanyi test for barbiturates, acid phosphatase test and tests for sulfonamide erytals. Classification and identification of certain streptococci, staphylococci and pathogenic fungi are included. While not without a few minor errors, this book should prove decidedly useful for the laboratory technician.

The Chemistry and Technology of Food and Food Products. Edit. by M. B. Jacobs. Vol. 1, Pp. 952 (\$10.50). Vol. 2, Pp. 890, (\$10.50). New York, Interscience Publishing Co., 1944.

This is an ambitious work attempting to cover the fields of the science and technology of the world's foods. The two volumes were written by 41 contributors and range from the physical chemistry of foods to the problems of pest control. In scope the ground covered is extremely wide. Actually one is amazed that so much knowledge is at hand dealing with food products and their manufacture since in everyday life little of

this information comes to our attention. The subject index of over 100 pages and the nearly 400 tables, numerous maps, pictures, and charts are extremely useful. For the physician, interested layman and technician alike these two volumes will prove invaluable because of the great wealth of information they contain.

Diet Manual. Prepared by the Department of Nutrition, University of Kansas Hospitals. Edited by Ruth Gordon, Pp. 92, (\$2.50). Lawrence, University of Kansas Press, 1945.

Although every practitioner has his own tried diets, often he wishes these were collected into an easily accessible and convenient form. It is generally burdensome to consult standard volumes on nutrition and dietetics for these diets. This volume was designed to fill this need. In general this has been done successfully. However, the fifteen page discussion of vitamins without a corresponding consideration of minerals and other food substances essential to health could have been reduced or altogether omitted. While there are minor omissions, the manual on the whole appears to be as complete as one may wish. All the major diseases are considered. The volume is to be recommended as a handy collection of standard diets. It should prove particularly useful for the interne and resident, as well as attending physician, in determining the diets to be ordered in particular instances. A happy thought was the inclusion of lists of foods to be avoided in each instance. The thorough index is helpful.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Medicofilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Medicofilm Service, Army Medical Library, Washington, D. C.)

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MOUTH AND ESOPHAGUS

CASSINELLI, J. F. AND TISCOMIO, R. E.: *Congenital atresia of the esophagus.* (*Arch. Pediat. Uruguay*, v. 15, p. 206, April 1944).

The authors describe two cases of congenital atresia of the esophagus. They believe that this malformation may be diagnosed accurately by means of radiologic studies. Knowledge of the existence of a clean-cut esophagotracheal sinus should make the physician extremely wary in suspecting congenital esophageal atresia. The syndrome is comprised of a history of regurgitation following feeding, cough, cyanosis, dyspnoea alternating with apnoea, and the abdomen distended, with tympanitis. The authors stress the differential diagnosis of this malformation from pulmonary disease. Included in this report are several roentgenograms. — D. J. Abolofia.

RICHARDSON, J. R.: *New treatment for esophageal obstruction due to meat impaction.* (*Ann. Otol. Laryngol.*, v. 54, p. 328, June 1945).

Impaction of the esophagus due to swallowing large pieces of meat is an occurrence in adults and children having either no teeth or few teeth. Usually the impaction occurs in an individual having a constriction of the esophagus, though it may occur in people with a normal esophagus. The esophagoscope has been used in the past to remove the impaction but this can be avoided by digesting away the meat. Papin solution is ingested and the enzyme is permitted to dissolve the meat by proteolysis. Operative procedures are unnecessary. Richardson reports successful enzymatic treatment in 16 out of 17 cases. The single failure was attributed to inability of the patient to retain the papin. — G. Klenner.

STOMACH

HORAN, H. J. and COMFORT, M. W.: *Inflammatory cyst of the stomach secondary to cholelithic disease. Report of a case.* (*Proceed. Staff Meet. Mayo Clinic*, v. 20, p. 237, June 1945).

A fifty year old patient who had previously had a cholecystostomy with complaints of gaseous distress, mild colicky attacks, nervousness, fatigue and insom-

nia was seen at the clinic. Roentgenoscopy revealed an extrinsic tumor of the stomach. At operation the subacutely inflamed gall bladder was found attached at its fundus to a cystic mass arising from the wall of the stomach. The gall bladder contained a stone impacted in the cystic duct. Partial gastrectomy with Billroth I type of anastomosis and a cholecystectomy were done. This represents a rare complication of cholelithic disease, being the only case so far described in the literature. —W. J. Snape.

BOWEL

PEARSON, R. J. B.: *Steatorrhea due to lymphatic obstruction.* (*Proceed Royal Soc. Med.*, v. 38, p. 385, May 1945).

Fat may be found in excess in the stools in a variety of conditions. It has been recognized that tropical sprue, idiopathic steatorrhea and coeliac disease have much in common with respect to symptoms. Some clinical investigators believe that these diseases really are identical. A somewhat similar symptom complex may develop as the result of obstruction of the lymphatic lacteals. Tuberculosis of the mesenteric glands and mesenteric lymph nodes is often associated with a history of steatorrhea.

In this paper Pearson presents three cases of obstruction of the lacteals in which the clinical features of steatorrhea were pronounced. Macrocytic anemia and sore tongue were present in two cases. Although failure for the absorption of fat was the main feature, it was apparent that the absorption of other food substances in addition to fat were also affected. — F. E. St. George.

PRATT, J. H.: *Perforations of the rectal wall by enema tips* (*Proceed Staff Meet. Mayo Clinic*, v. 20, p. 277, August 8, 1945).

Perforation of the rectum by enema nozzle tips is an emergency which occurs rarely. Twenty cases have been reported in the literature. The patients were either past sixty years of age or were pregnant women. Not much force need be applied to perforate the rectum and the conscious person feels no undue pain during the perforation. Mortality rates have been high but the introduction of the sulfonamides and early surgery will

no doubt bring about a reduction in the number of deaths in the future.

The injury resulting from the perforations is of a complicated nature since in addition to the tear in the rectal wall there usually is also introduction of irritating fluids into the abdominal cavity. The pains experienced by the patient are due to the action of these fluids in the abdominal cavity. Acute tenderness and rigidity of the lower abdomen are evident.

Operation consists of finding the tear and suturing it. Sulfathiazole is left in the abdominal cavity. Closure is without use of drainage. Tetanus-perfringens anti-toxins should be administered. Surgery must be instituted before the fourth or fifth hour since a delay of seven hours is nearly always fatal.—G. N. N. Smith.

LIVER AND GALLBLADDER

KELSEY, M. P. AND COMFORT, M. W.: *Occlusion of hepatic veins: review of twenty cases.* (*Arch. Intern. Med.*, v. 75, p. 175, March 1945).

The Mayo Clinic records show 20 cases of occlusion of the hepatic veins as proved by autopsy. In only four cases were there symptoms and in three of these the occlusion was the main cause of death. In every case the occlusion was due to thrombosis. Relatively rapid increase in the size of a liver which is tender and epigastric pain extending to the back should make the physician aware of hepatic vein thrombosis as a possible diagnosis. The congested liver due to obstruction of the hepatic veins may perhaps be visualized by peritoneoscopy to distinguish the condition from liver cirrhosis or liver cancer. Acute occlusion of the hepatic veins may be mistaken for acute pancreatitis. However, the rapid increase in liver size, the profound disturbance in liver function and the level of the serum amylase serve as distinguishing points. The terminal stage of the chronic forms of the disease is similar to the early stage of the acute form.—G. N. N. Smith.

MCKIBBON, J. P. AND McDONALD, J. R.: *Significance of polymorphonuclear leukocytes in gall bladder.* (*Proc. Staff Meet. Mayo Clinic*, v. 20, p. 167, May 1945).

The purpose of this paper is to attempt a correlation, if possible, of the clinical course and the histologic structure of gall bladders. Histologic examination often reveals polymorphonuclear leukocytes in grossly appearing normal gall bladders. Comparison was made between the following groups: first, non-calcareous, thin-walled gall bladder; second, "strawberry" gall bladder; third, calcareous gall bladder; fourth, dog's gall bladder; fifth, fetal gall bladder; sixth, sections of appendices removed without pathology existent; seventh, sections of jejunum from a dog; and eighth, sections from non-inflammatory jejunal segments.

Polymorphonuclear leukocytes were found in the capillaries and pericapillary area of both the calcareous and the thin-walled non-calcareous gall bladder. The

appendices were devoid of these leukocytes but the jejunum had a picture similar to the gall bladder. The fetal gall bladders were also free from the picture of the typical adult gall bladder. From these results it was concluded that the presence of polymorphonuclear leukocytes is not necessarily indicative of an inflammatory process but that they may be concerned with metabolic functions.—W. J. Snape.

HAVENS, W. P., JR.: *Properties of the etiologic agent of infectious hepatitis.* (*Proc. Soc. Exper. Biol. Med.*, v. 58, p. 203, March 1945).

The etiologic nature of the icterogenic agent which produces infectious hepatitis is unknown but is believed to be a virus. Bacteriologically sterile serum inoculated parenterally to human volunteers has resulted in transmission of the disease. In homologous serum jaundice and in post vaccinal jaundice the causative agent has been shown to be filterable virus. In the present experiments it was demonstrated on human volunteers that the icterogenic agent in infectious hepatitis is likewise a filterable virus. The virus withstands heating to 56 degrees C. for 30 minutes and can be transmitted by serial passage in humans. Oral, intranasal, subcutaneous and intracutaneous routes of administration of the infective material were used.—M. H. F. Friedman.

ULCER

STORER, E. H., THORNTON, T. F., AND DRAGSTEDT, L. R.: *Supra-diaphragmatic section of the vagus nerves and gastric motility in patients with peptic ulcer.* (*Proc. Soc. Exper. Biol. Med.*, v. 59, p. 141, June 1945).

This paper is a preliminary report of some observations that have been made on the motility of the stomach in 38 patients both before and after operation. The authors have concluded that when the empty stomach of the patients with peptic ulcer is examined by the balloon technic, it usually displays hypertonicity and hypermotility. Also they observed that bilateral section of the vagus nerve in patients with peptic ulcer decreases the gastric tonus and hunger contractions of the empty stomach.—I. H. Dougherty.

MISCELLANEOUS

ROGERS, H. M., AND HALL, B. E.: *Primary splenic neutropenia.* (*Arch. Intern. Med.*, v. 75, p. 192, March 1945).

The present case constitutes the eighth of primary splenic neutropenia to be reported in the literature. Thrombocytopenia, splenomegaly and myeloid hyperplasia are the most outstanding features of the disease. The patient was cured by splenectomy. Hepatic damage associated with splenic neutropenia was found but this complication was not considered as contraindicating splenectomy. Thrombosis of the splenic vein (Banti's disease), congenital hemolytic icterus and thrombocytopenia purpura are indications for removal of the spleen.—G. Klenner.

A Nomogram for the Preparation of Insulin-Protamine Zinc Insulin Mixtures

By

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WHEN protamine-zinc-insulin was introduced into the pharmacopeia, it was hoped that this new drug would permit diabetics to control their disease with but a single daily injection. However, it was soon clearly established that this hope was not to be realized. Various schemes involving the simultaneous injection of the new insulin and the old unmodified product were tried. These were very successful but the patients still required two sticks with the needle and the use of two different insulins by the same patient sometimes led to disastrous errors. The author recalls a patient who was supposed to take 80 units of P.Z.I. and 20 of regular insulin each morning. She made a mistake one day and had a very severe reaction an hour later. For some time thereafter, it was felt that protamine-zinc-insulin should be used only for the comparatively few fairly mild cases that could be controlled satisfactorily with one injection a day. Most cases were treated with two injections of regular or crystalline insulin administered before breakfast and supper.

During the past few years, a number of investigators showed that fairly predictable results could be obtained by combining the two insulins in the same syringe. These early results are admirably summarized by Peck (1). He then investigated the behavior of mixtures of regular (or crystalline) with protamine-zinc-insulin and he devised a table to show the content of slow-acting and quick acting insulin in such mixtures (1, 2).

The author has used combinations of the two commercial forms of insulin for all diabetics under his care who required more than about 30 units per day. The obvious advantage of administering the entire day's requirement in a single injection seemed to outweigh any objections based on the inconvenience of drawing the insulin from two vials. The 2:1 mixture (two parts of regular to one of protamine-zinc-insulin) seemed to strike a fair average and it was used in all cases. However, each diabetic is a law unto himself and this Procrustean prescription led to serious difficulties. Not a few of the patients had severe hypoglycemic reactions at unpredictable times although they spilled sugar during other parts of the day. It was soon realized that a more flexible method of combining the two insulins was necessary. The following scheme was gradually evolved to fill this need.

The accompanying nomogram gives all the information required to handle any diabetic. It consists of six scales. From above downward, these are —

Q — a scale indicating units of quick acting insulin.
R — a scale indicating units of regular (or of crystalline) insulin.

D — a scale indicating the entire dose for the day.
S — a scale indicating units of slow acting insulin.
P — a scale indicating units of protamine-zinc-insulin.

M — a triple scale indicating the proportions of the mixture. The first graduation gives the volume of protamine-zinc-insulin to be mixed with 5 cc. of regular insulin in order to prepare the patient's special mixture. This will be explained a little later. The second *M* scale gives the ratio of regular to protamine-zinc-insulin in the mixture. The third scale gives the percentage of slow insulin in the mixture. The fact that the quick and slow insulins exist only after mixture is indicated by lettering their scales in italics.

The patient is first standardized with separate injections of regular and protamine-zinc-insulin given at the same time but in different sites. Although, as Peck has pointed out, the time-activities of the quick and slow components in mixtures are not the same as those of regular and protamine-zinc-insulin when administered separately, we may, as a first approximation, consider them to be equivalent. In most cases the mixture made on this assumption will work very well. If not, we can juggle the doses a bit to make the adjustment better.

Having thus determined the amounts of quick and slow insulins we wish to administer, we place a ruler on the chart so that its edge passes through the points on the *Q* and *S* scales that represent these respective values. The edge will cut the *R* and *P* scales to give the amounts of regular and protamine-zinc-insulin which, if mixed in the same syringe and injected together, will furnish the desired amounts of quick and slow insulins. We then try this mixture for a few days. After any slight adjustment is made, we proceed to make up a special insulin mixture.

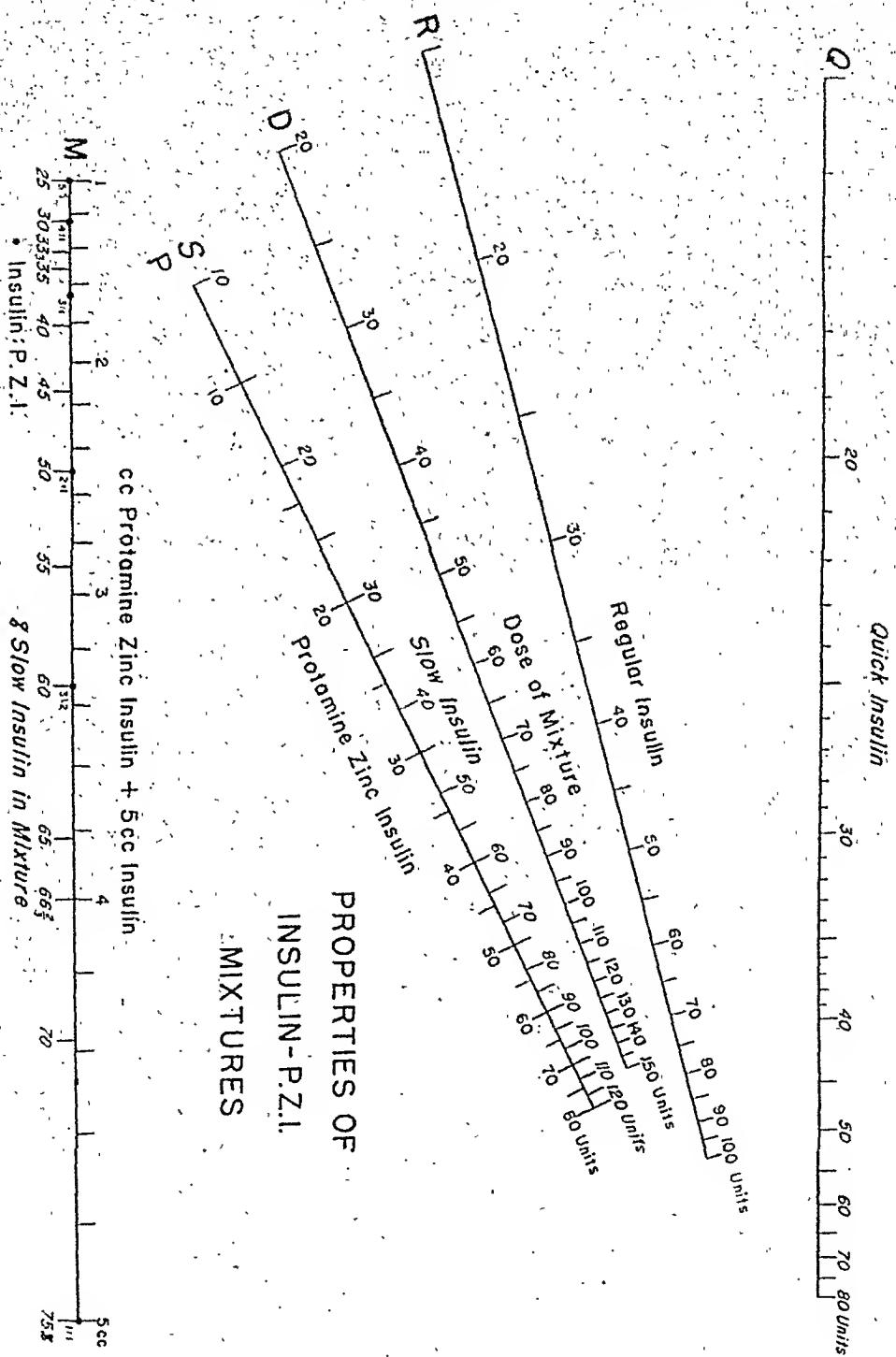
It is no easy task, even for a trained physician or nurse, to aspirate the two insulins from the separate vials without contaminating one insulin with the other. The first vial usually gives no trouble but the partial vacuum in the second bottle tends to suck the contents of the syringe into it. We may get around this difficulty by first injecting a little air into the second vial, removing the syringe and needle and then aspirating from the first vial and later taking up the second variety of insulin. This is obviously a needlessly complicated procedure. Furthermore it does not remove the principal objection against the use of two different insulins by the same patient — the danger of switching the doses.

It seems desirable to furnish the patient with but one kind of insulin. This cuts down the possibilities of error in dosage since but one measurement has to

be made. Furthermore, reproducibility is better since no error due to incomplete mixture is introduced.

For the preparation of this special insulin, we require a vial each of regular and protamine-zinc-insulin of the same strengths, an empty vial and a 5 cc. graduated syringe. Under sterile precautions, 5cc. of the regular insulin are aspirated into the syringe and then injected into the empty vial. Then the entire remainder of the regular insulin is taken up into the syringe. We discard

the slight amount of insulin in excess of 5 cc. that will be present and then inject the 5 cc. portion back into its original container. We now have two vials each containing just 5 cc. of regular insulin and the intact vial of protamine-zinc-insulin. The intersection of the ruler with the upper M scale is then noted. This volume of protamine-zinc-insulin is aspirated from the vial and injected into each of the other two half filled vials. This gives us two vials each containing



Nomogram for Preparing Insulin - P. Z. I. Mixtures

a little less than 10 cc. of a special mixture and the remainder of the protamine-zinc-insulin. The latter can be saved for future mixtures and the only waste is the slight amount of regular insulin in excess of 10 cc. that is usually placed in the bottle by the manufacturer. The patient then takes one dose per day equal in amount to the value indicated by the intersection of the ruler with the D scale. This is, of course, equal to R plus P or Q plus S. The two vials of special insulin will usually be just about the correct amount to last the patient until his next visit. Of course, greater amounts can be prepared once the patient is well standardized.

We may go about the standardization in another way. We first decide on the proportions of quick and slow insulins we wish to administer. This is located on the lowest M scale. Then the total dose for the day is located on the D scale and the edge of the ruler determines the amounts of regular and protamine-zinc-insulin required for our test dose. After we are satisfied that the patient is properly adjusted, we make up his mixture according to the method outlined above. Either of these methods makes the marketing of special

mixtures or of insulin in partially filled vials unnecessary.

These methods will become clearer by giving numerical examples. Suppose we wish to give 40 units of slow insulin and 25 of quick. Each dose is made from 38 units of regular and 27 of protamine-zinc-insulin. If that is satisfactory, we prepare the special insulin from 5 cc. of regular and 3.5 cc. of protamine-zinc-insulin and the patient takes 65 units per day. Or, suppose we wish to administer 70 units of insulin 65 per cent of which are the slow variety. The test dose is made from 39 units of regular and 31 of protamine-zinc-insulin and the final mixture is made from 5 cc. of regular insulin and 3.8 cc. of P.Z.I.

The middle M scale (small figures) gives the proportions that are found in Peck's table. It is obvious that the chart gives a wider selection.

These scales are based on the formulae —

$$S = P \times 3/2$$

$$Q = R - \frac{1}{2}P$$

$$D = R + P = Q + S$$

which fit the figures in Peck's table (1).

R E F E R E N C E S

1. Peck, F. B., Mixtures of Insulin and Protamine-Zinc-Insulin, *Ann. Int. Med.*, 18:177, 1943.

2. Peck, F. B., Action of Insulin, *Proc. Am. Diab. Assoc.*, 2:60, 1942.

Metabolic Abnormalities in Obesity: A Statistical Survey

By

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ACCORDING to prevalent opinion, metabolic abnormalities in obesity are inconsistent and of no significance (2,12). These sweeping statements are based on data obtained by complicated methods of apparently great accuracy and hence have found ready acceptance. Close analysis of the evidence, however, reveals that conclusions were arrived at either after the study of a single case (4), or from the mean of a statistically insignificant series. Thus, the variations of blood lipids were studies on three patients, the respiratory quotient on a series of seven, while an often quoted paper on the determination of the specific dynamic action of proteins is based on the study of eight obese patients and ten controls (16). The numerical paucity of this material is aggravated by the fact that the results were presented simply in the form of averages without due consideration of the representativeness of the given sample, the distribution of the individual values about the mean, or other variables avoidable by the use of standard statistical methods.

In consideration of other evidence which, contrary

to these assumptions, points to the importance of metabolic disorders in the pathogenesis of obesity, it seemed desirable to study the metabolic status of obese patients on a series sufficiently large to permit statistically valid interpretation. Our survey is based on material which had been obtained in the course of routine diagnostic studies of clinic patients. The findings in 100 consecutive unselected cases of obesity were compared with those in another group of 100 consecutive obese cases in which the clinical diagnosis of pituitary disease had been arrived at. Further comparisons were made between these two main groups and several subgroups selected according to fat distribution or age.

The data surveyed in this study include: basal metabolism, specific dynamic action of proteins, fasting blood sugar, blood uric acid, lymphocyte count, 24 hour urine volume, NaCl excretion and salt tolerance.

The specific dynamic action was studied by the sample method, comparing the basal metabolic rate with the oxygen consumption two hours after ingestion of a small protein meal (the white of three eggs). Whatever the inherent shortcomings of the sample method may be, the use of the same method in a large

number of cases permits comparison and statistical evaluation of the data. The salt tolerance was determined by comparing the urinary excretion during two 24-hour periods in which food and water intake was identical except for the test dose of ten grains of NaCl and 250 cc. of water given on the morning of the second day. Sugar tolerance tests are not included in this survey because their number in the group investigated was not large enough for statistical evaluation.

The statistical significance was determined according to the equation:

$$R = \frac{M_a - M_b}{\sigma}$$

$$\text{age} = \frac{\text{days}}{\text{Nb}}$$

When $M =$ the means,

$\sigma =$ standard deviation

$N =$ size of sample

$a, b =$ designates samples compared

R represents the ratio of the difference of the means to the standard error of their difference. According to probability theory, if R equals 2.5, the odds are about 80:1 against the difference occurring merely by chance. While R equals 2 is widely used, we have insisted on the stricter R equals 2.5 as an indicator of statistical significance.

BASAL METABOLISM

Determination of the basal metabolism in 100 unselected, consecutive cases of obesity showed a mean of minus 6.33 plus or minus 0.8. These 100 cases were divided into three groups according to fat distribution:

1. 26 cases of general obesity with even fat distribution;

2. 38 cases of obesity with regional deposits (in the nape of the neck, in the trochanteric region, "buffalo" type with full moon face and prevalence of fat over the trunk, obesity of the lower half of the body);
3. 36 cases of obesity with regional fat deposits of the "pituitary" type (girdle, apron, special pads on the insides of thighs and upper arms).

The mean of the first group was minus 5.6 plus or

Frequency Distribution of Values of Basal Metabolic Rate in 100 Consecutive Obese, with Breakdown into the 3 Constituent Groups.

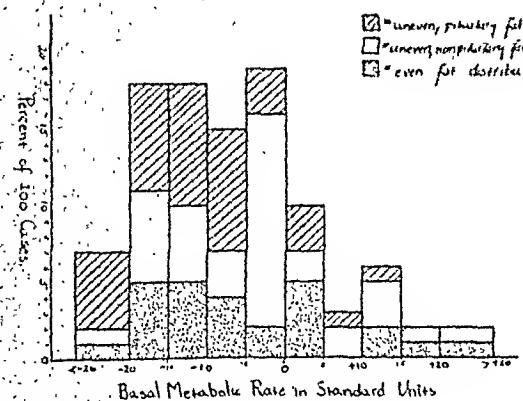


CHART NO. I

minus 1.5; the difference, compared with the mean of the 100 unselected cases, is not significant. The mean of the second group was minus 4.3 plus or minus 1.5; the difference as compared with the main group is just below the standard of statistical significance (R , equals 2.4). The third group shows a mean of minus 10.5 plus or minus 1.1; the difference between this figure and the mean of the main group is statistically significant (R equals 3.1). The range of distribution of low and high metabolic rates in the subgroups is presented on Chart No. 1.

In 50 consecutive cases of obesity in juveniles (age

Distribution of B.M.R. in various types of obesity: juvenile, adult unselected, adult pituitary.

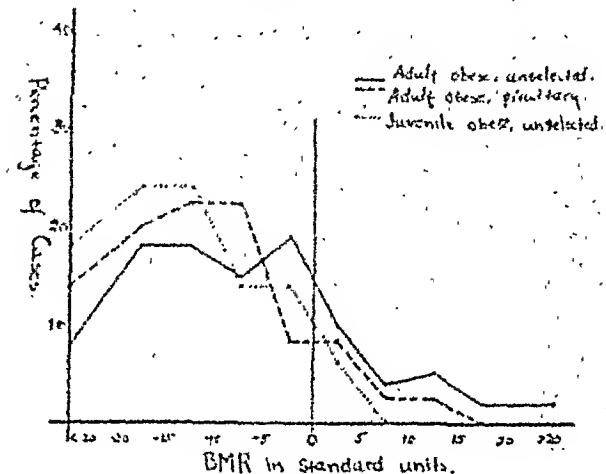


CHART NO. II

TABLE I
Statistical values and Frequency Distribution of the Basal Metabolic Rate in Various Groups of Obese Patients.

- a. 100 consecutive obese patients, with breakdown.
b. 50 consecutive juvenile obese patients.

Value of B. M. R.	100 Consecutive Obese Patients	26 (of the 100) with even fat distribution	31 (of 100) uneven, nonpituitary fat distribution	16 (of 100) uneven, pituitary fat distribution	50 juvenile obese
Mean	-6.33	-5.6	-4.3	-10.5	-12.7
Standard error (± 1)	0.80	1.0	1.5	1.1	1.1
Standard deviation (σ)	8.03	8.06	9.3	6.6	7.8
Distribution in %					
Less than -20	7	4	3	14	8
-19 to -15	18	19	16	20	24
-14 to -10	18	19	13	22	24
-9 to -5	15	15	8	22	14
-4 to 0	19	7.5	37	8	14
1 to 5	10	19	5	8	6
6 to 10	4	0	5	3	0
11 to 15	5	7.5	8	3	0
16 to 20	2	4	3	0	0
Over 21	2	4	2	0	0

10 to 17 years), the basal metabolic rate showed a mean of minus 12.7 plus or minus 1.1, presenting a statistically significant difference (R equals 4.6). This mean compares more nearly to that of the group with pituitary fat distribution, a similarity which increases if we compare the frequency distribution in the juvenile, the clinically pituitary and the unselected group of obesity (Chart No. II).

Thus, in the juvenile group the greatest concentration is below minus 10 while in the pituitary group slightly more cases are found in the range between minus 10 and 0. In the unselected group considerably fewer cases occur in the low range while a substantial part of the group is above 0 (Table I).

SPECIFIC DYNAMIC ACTION OF PROTEINS

The difference between the basal metabolic rate and the rate two hours after the ingestion of protein yields a mean of 8.28 plus or minus 0.68 for the 100 unselected cases of obesity. Considerable differences are noted in the three subgroups of even, uneven and pituitary fat distribution, respectively: in the even group, the mean is 11.0 plus or minus 1.77; this differs significantly from the main group (R equals 3.7). The two other, more important subgroups, were enlarged to 100 cases each by the addition of consecutive cases of similar type from the clinic records. In the 100 cases with uneven fat distribution, the mean was 11.1 plus or minus 0.85, showing a significant difference from the 100 unselected cases (R equals 2.6).

In the 100 obese cases with pituitary fat distribution, the mean was 4.17 plus or minus 0.42, showing a highly significant difference from the means of the other groups (R equals 2.9).

A survey of 65 consecutive cases of obesity in juveniles showed a mean of 4.9 plus or minus 0.76, significantly different from the mean of the unselected groups (R equals 3.3), but rather similar to that obtained in pituitary obesity.

Further comparisons were made with a group of 35 consecutive obese cases of natural or surgical menopause, or striking hypogonadal characteristics. The mean

in this group was 15.9 plus or minus 1.43; the difference between this figure and the means of both the unselected and the pituitary group is statistically significant (R equals 4.9).

The importance of the means presented is enhanced by the peculiarities of distribution as demonstrated on Table 2 and Charts III and IV.

FASTING BLOOD SUGAR

In the 100 unselected cases of obesity calculation of the blood sugar values in mgm. % gave a mean of 101 plus or minus 1.35; a practically identical figure, a mean of 103 plus or minus 2.2 was obtained in the obese cases with even fat distribution.

Comparison of these values with those of pituitary obesity or the juvenile group showed significant differences (R equals 2.9, R equals 3.8 respectively); In 100 cases of pituitary fat distribution, the mean was 94.4 plus or minus 1.6, and 93.6 plus or minus 1.58 in 65 juvenile cases.

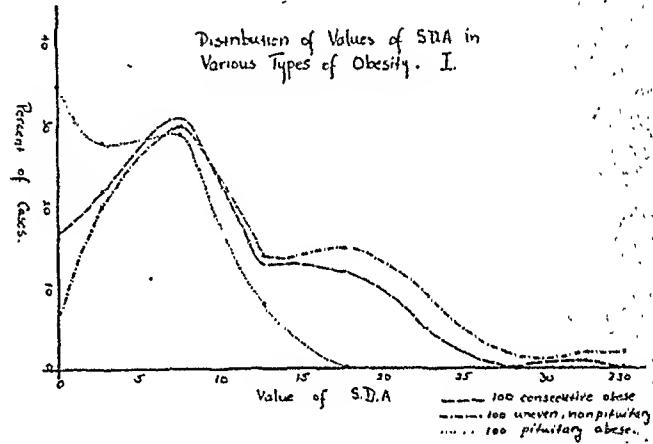


CHART NO. IV

TABLE II
Statistical Values and Frequency Distribution of the Specific Dynamic Action in Various Groups of Obese Patients.

S. D. A.	100 Consecutive Obese	22 Obese, Even Fat Distribution	100, Uneven, Nonpituitary Obese	100, Uneven Pituitary Obese	65 Juvenile Obese	35 Hypogonadal Or Menopausal Obese
Mean	8.28	11.0	11.1	4.17	4.9	15.9
Standard Error (\pm)	0.68	1.77	0.85	0.42	0.76	1.43
Standard Deviation (σ)	6.8	8.3	8.5	4.2	6.1	8.5
Distribution in %	0 - 17	4.5	7	35	36	0
1 - 5	22	18	20	28	38	8.5
6 - 10	31	32	30	29	14	23
11 - 15	13	18	14	8	10	20
16 - 20	12	23	15	0	10	28
21 - 25	4	4.5	9	0	2	6
26 - 31	0	0	2	0	0	8.5
31 - 35	1	0	2	0	0	3
Over 36	0	0	2	0	0	3

Distribution of Values of SDA in Various Types of Obesity. II.

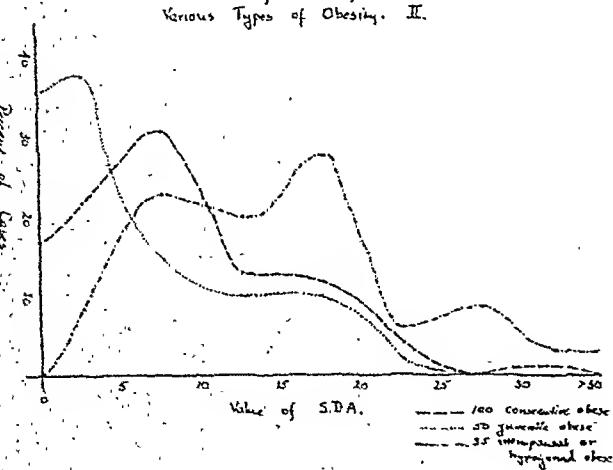


CHART NO. III

TABLE III

Statistical Values and Frequency Distribution of the Fasting Blood Sugar in Various Groups of Obese Patients.

	100 Consecutive Cases	100 Pituitary Cases	100 Juvenile Cases	100 Even Fat Distribution
Mean	101.5	93.9	93.6	101
Standard error (\pm)	1.35	1.6	1.58	1.2
Standard deviation (\pm)	13.5	13.2	12.4	16.5
Distribution in %				
60 - 69 mgm. %	1	3	0	0
70 - 79	1	7	8	6
80 - 89	11	33	34	9
90 - 99	27	23	24	27
100 - 109	33	16	20	41
110 - 119	15	13	8	14
Over 120	8	6	6	8

Distribution of Blood Sugar Values in Various Types of Obesity

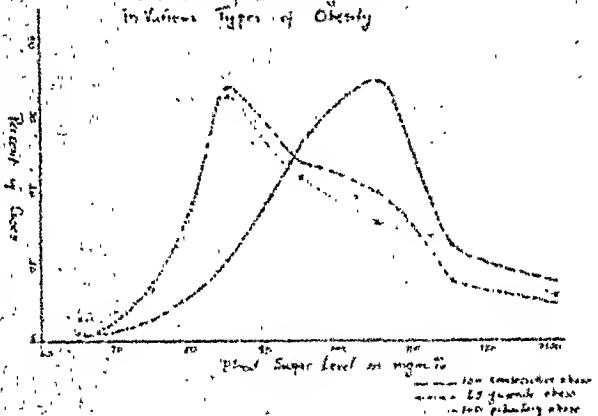


CHART NO. V

The absolute differences between these figures, though statistically significant, at first glance, seem rather small. Their importance becomes apparent by comparing the frequency distribution in the various types of obesity as presented on Table 3 and Chart V.

The tabulation clearly shows that a non-negligible part of the blood sugar values is abnormal, either being below .80 or above 115 mgm. %. The truly hypoglycemic cases are definitely more numerous in the pituitary and juvenile groups, with opposite though less impressive differences in the hyperglycemic bracket. More significant is the concentration in the range between 80 and 90 mgm. % in the pituitary and juvenile groups whereas the peak of the unselected group is reached in the range of from 100 to 109 mgm. %.

BLOOD URIC ACID

Determination of the blood uric acid in 100 unselected cases of obesity, expressed in mgm. % gave a mean of 3.65 plus or minus 0.08. The mean blood uric acid in the group with even fat distribution was 3.6 plus or minus 1.79; the difference is not significant.

TABLE IV

Statistical Values and Frequency Distribution of the Fasting Blood Uric Acid Level in Various Groups of Obese Patients.

	100 Consecutive Cases	100 Pituitary Cases	100 Even Fat Distribution
Mean	3.63	3.97	3.60
Standard error (\pm)	0.08	0.09	1.79
Standard deviation (\pm)	0.78	0.53	0.84
Distribution in %			
Less than 3.1 mgm. %	35	9	27
3.1 - 3.5	36	23	32
3.6 - 4.0	39	25	9
4.1 - 4.5	22	24	23
Over 4.5	9	19	9

Frequency Distribution of Blood Uric Acid Values in Various Types of Obesity

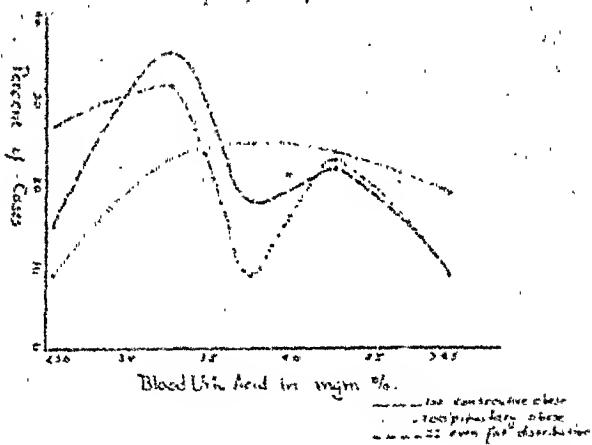


CHART NO. VI

Distribution of Values of Lymphocyte Counts in Cases of Obesity

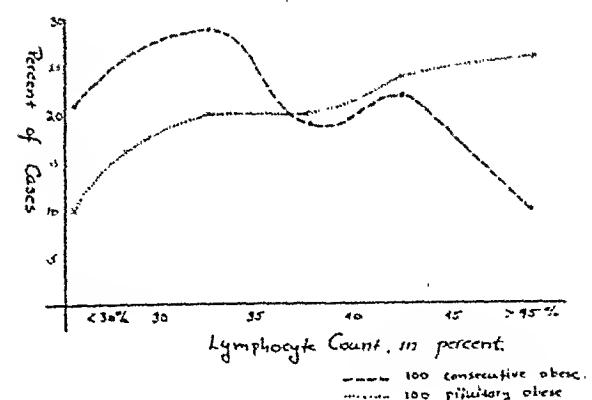


CHART NO. VII

TABLE V

Statistical Values and Frequency Distribution of the Lymphocyte Count in Various Groups of Obese Patients.

Lymphocyte count — per cent of total white count	100 Consecutive Obese	100 Uneven, Pituitary Obese
Mean	35.4	40.0
Standard error (\pm)	0.7	0.63
Standard deviation (s)	7.0	6.27
Distribution in %		
21-30 %	21	10
31-35 %	29	20
36-40 %	19	20
41-45 %	21	24
Over 45 %	10	26

In the 100 cases of pituitary obesity, the mean was 3.97 plus or minus 0.09, a statistically significant difference (R equals 2.8).

The weight of the differences observed is increased by the variation in distribution which shows that low values occur less often and high values (above 4.5) much more often in the pituitary than in the other two groups (Table 4, Chart VI).

LYMPHOCYTOSIS

Calculation of the percentage of lymphocytes in 100 unselected cases of obesity gave a mean of 35.4 plus or minus 0.7. In 100 consecutive cases of pituitary obesity the mean was 40.0 plus or minus 0.63, a statistically significant difference (R equals 4.5). Tabulation of distribution on Table 5 and Chart VII shows clearly that low lymphocyte values are rarer and high values more common in the pituitary group.

TABLE VI

Retention of Sodium Chloride During the Course of the Salt Tolerance Test in Various Groups of Obese Patients.

NaCl Retention	100 Consecutive Obese	100 Uneven, Pituitary Obese
Mean	6.0	7.5
Standard error (\pm)	0.38	0.40
Standard deviation (s)	3.8	3.97
Distribution (in %)		
0 or Less	8	3
0.1 to 3.0	15	10
3.1 to 6.0	28	20
6.1 to 9.0	25	26
9.1 to 12.0	16	26
Over 12.0	8	15

URINARY VOLUME AND SALT EXCRETION

In the 100 unselected cases of obesity, the mean of the urinary volume, calculated in cc. was 980 plus or

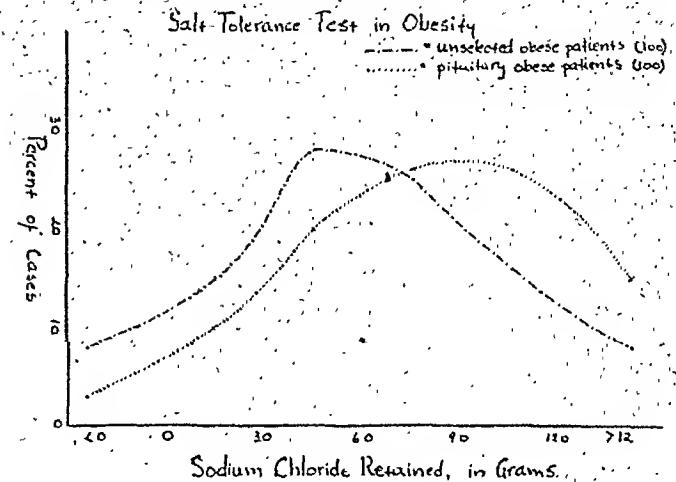


CHART NO. VIII

minus 42.0 while in the 100 cases of pituitary obesity the mean was 1090 plus or minus 55.2. The difference between the two figures, though apparently substantial (110 cc.), is statistically not significant, obviously because the range of values included in the survey is too extreme. The excretion of NaCl in the 100 unselected cases, expressed in Gm. gave a mean of 8.6 plus or minus 0.45. A significant difference (R equals 4.5) was obtained by comparing this figure with the mean of 9.5 plus or minus 0.49, representing NaCl excretion in the 100 cases of pituitary obesity.

TABLE VII

Retention of Water (as seen by Urinary Volume) During the Course of the Salt Tolerance Test in Various Groups of Obese Patients.

Water Retention	100 Consecutive Obese	100 Uneven, Pituitary Obese
Mean	111	191
Standard error (\pm)	34.3	34.8
Standard deviation (s)	343	348
Distribution (in %)		
Less than -250 cc.	14	12
-250 to 0 cc.	18	12
1 to 250 cc.	33	31
251 to 500 cc.	27	30
Over 500 cc.	8	15

SALT RETENTION TEST

Studies of the urinary volume and salt excretion after intake of 10 Gm. of NaCl and 250 cc. water showed a retention of water in the 100 unselected cases of obesity with a mean of 111 plus or minus 34.3.

In the 100 cases of pituitary obesity, the retention appeared to be even greater with a mean of 19.1 plus or minus 34.8. Nevertheless, the difference again is not significant, apparently for the same reason which made the urinary volume of the preceding 24 hour control period unsuitable for statistical evaluation.

Excretion of NaCl after performance of the salt tolerance test showed significant differences (R equals .88): NaCl excretion expressed in Gm. in the 100 unselected cases of obesity gave a mean of 6.0 plus or minus 0.38 whereas, the mean in the 100 cases of pituitary obesity was 7.5 plus or minus 0.40.

The importance of salt retention in the course of the salt tolerance test is emphasized by the range of distribution as shown on Table 6 and Chart VIII.

The figures as well as the curves show clearly that absence of or slight retention is less often met with in pituitary obesity, in which extremely high values occur far more often than in the unselected group.

A trend to concomitant water retention is demonstrated by the distribution of ranges of urinary volumes in both the unselected and pituitary groups of obesity in which retention appears in 68 and 66% of the cases respectively (Table 7 and Chart IX).

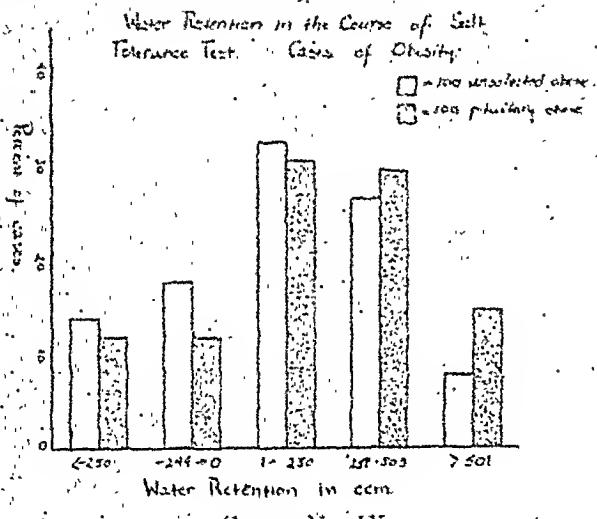


CHART No. IX

DISCUSSION

The survey presented shows, first of all, that an abnormal metabolic status is demonstrable in a group of 100 unselected, consecutive cases of obesity. According to Chart I, a basal metabolic rate of minus 10 or less is noted in 43% of these cases. While the mean of minus 6.33 is within the range considered as normal, it cannot be overlooked that the rates are abnormally low in a considerable percentage of the cases. The low basal metabolic rate is definitely more prevalent in the group which includes a high percentage of pituitary disease. The mean of the basal metabolic rate of minus 10.5 and minus 12.7 respectively is lower than the value ordinarily considered as the lower limit of the normal range. The abnormality of the basal metabolic rate is even more apparent if the distribution of the

material is examined, for it shows that in both groups 56% are below the minus 10 level.

It is immaterial from the statistical viewpoint whether the basal metabolic rate is calculated according to weight, height, age and sex, or on the basis of the "ideal weight." Our figures are presented only for their relative significance but in this sense they clearly show the prevalence of lower metabolic rates both in the juvenile group and in patients stigmatized by pituitary fat distribution.

Our figures are in accord with some reports by earlier investigators. Thus, Boothby and Sandiford (1) who studied the basal metabolic rate in 58 cases of "hypopituitary" obesity, found the rate below minus 10 in 53.5% of their cases. A lower metabolic rate in pituitary obesity had been claimed even earlier by Means, et al. (2). Rowe (3), who compared the basal metabolic rates in two groups of obesity, found an average of minus 15 in the pituitary group and minus 6 in other cases of obesity.

Our figures expressing the specific dynamic action of proteins are similar to earlier findings (8) based on 264 cases of pituitary disease and 85 controls. In the latter, the mean was 16.8; in the pituitary group, consisting mostly, but not exclusively, of obese cases, a mean of 3.8 was calculated; the group includes four cases of pituitary tumor with high values for the specific dynamic action of proteins and a mean of 35. In a subsequent study of 200 cases (5), the following figures were presented:

No. of Cases	Diagnosis	Mean
11	Controls	13.0
29	Thyroid Disease	13.8
20	Menopause	17.0
6	Pituitary Tumors	24.8
134	Hypopituitarism	3.0

Our mean of the unselected obese group is lower than the figure previously reported as average in normal controls. This may be due to the heterogeneous nature of the group studied which includes menopausal cases with a high specific dynamic action as well as a large number (35%) of cases of pituitary disease with a low specific dynamic action of proteins. Our mean of 4.17 in the latter group compares favorably with the figure of 3.8 in Goldzieher and Gordon's survey (8). The mean of the juvenile group (4.9) comes fairly close to that of the pituitary group; the slight increase is apparently due to the high specific dynamic action of proteins obtained in a few cases of hypersecretory pituitary tumors. The high specific dynamic action of proteins of the hypogonadal group (15.9) closely approaches the figure of 17.0 obtained in the menopausal group (5).

The mean of the fasting blood sugar values is within the normal range in all groups, yet the means of the pituitary and juvenile groups are significantly lower than that of the unselected group. The distribution curves, however, bring out clearly that the fasting blood sugar is not infrequently abnormally low in obesity, especially in the juvenile and pituitary

groups. The preponderance of values between 80 and 90 mgm. % in the juvenile and pituitary groups is important; although such figures are generally not considered to be pathological, determination of sugar tolerance in such cases frequently reveals a flat curve with a hypoglycemic dip three or four hours after the ingestion of carbohydrate. Similar observations were made by Rony (13). Thus, fasting or post-prandial hypoglycemia is not unusual in obesity and accounts either for an increased hunger for carbohydrates or for an abnormal utilization of sugar in the body. The occurrence of an abnormally high fasting blood sugar is well known in the obese; a return to normal levels is frequently observed following weight reduction. Thus, it may be justifiably concluded that obesity is the cause of hyperglycemia, at least, in some cases. Irrespective of such conclusions, the hyperglycemic state can not be immaterial to the obese patient, for it represents a link in the chain of events which eventually lead to increased deposits of fat.

The mean of the blood uric acid in unselected cases of obesity (3.65) is definitely higher than the average encountered in an unselected hospital population where the mean is supposed to be within the range of 2.5 to 3.5 mgm. % (10). A general trend to increased values in pituitary disease was observed by Rowe (15) who calculated a mean of 3.8 mgm. % as compared with 3.5 mgm. % in his other material. The prevalence of a high uric acid in pituitary disease, irrespective of obesity, was pointed out before (6,7), but its association with obesity in general and especially with obesity of the pituitary type is first shown by our statistics. The relationship of hyperuricemia to the problem of obesity is not yet understood but it seems to suggest a disturbance in hepatic function.

The relative (and usually also absolute) lymphocytosis shown by our statistics is in accord with the observation that an increased lymphocyte count is a general symptom of practically all endocrine disorders (6). As the normal range of the lymphocyte count, 21 to 30% (16) or 25 to 33% (17) are widely accepted. Recent textbooks of Hematology (18) mention that "lymphocytosis occurs inconstantly in hyperthyroidism, hypothyroidism, diabetes and obesity". Our mean of 35.4% confirms the view that lymphocytosis prevails in obesity but particularly, in the hypopituitary type, in which the mean of 40% shows a statistically significant increase. While an abnormal increase of lymphocytes in the blood might be readily appreciated in thyroid or adrenal disease in which the involvement of the lymphatic tissue is established, the contention that lymphocytosis is a symptom of pituitary disease has acquired support only recently. The investigation of Dougherty and White (3) showed that lymphopenia is the specific response to the injection of adrenotropic pituitary extracts permitting the conclusion that "regulation of the numbers of the blood lymphocytes is under pituitary control."

Oliguria and water retention are among the well known symptoms of obesity; their association with retention of NaCl is also well established. Our statistical

figures are well in accord with these views. Our mean of 980 cc. of the urinary volume is somewhat lower than previously reported figures (15). However, in a small group of carefully studied cases of pituitary obesity, Rowe (15) calculated an even lower average urinary volume (820 cc.). According to our charts the group of obese patients includes a majority with low urinary volume, but also a sizeable minority, the urinary excretion of which is well above normal. Frequency and degree of polyuria seems to be even higher in pituitary obesity. The mean salt excretion is somewhat below the normal average in the unselected obese group and approximates the normal even more closely in the pituitary group. The salt tolerance test, however, shows retention of NaCl with a mean of 6 Gm. (60% retention) in the unselected obese and 7½ Gm. (75% retention) in the pituitary group. In order to demonstrate statistically the simultaneous, clinically unmistakable retention of water, one would have to survey a much larger series in which a few cases of polyuria would not produce such an excessive coefficient of variation.

The pathogenesis of the disturbed salt and water metabolism in obesity and especially, in the pituitary type of obesity, is still obscure, but it is certain that several endocrine factors contribute their share (9). It might be questioned whether one or the other endocrine gland is more important in determining the tendency to water and salt retention and especially, the response to the salt tolerance test; it is more likely, however, that the metabolic disturbance expresses the sum total of varied endocrine influence.

SUMMARY

The metabolic status of 100 unselected cases of obesity was surveyed and compared with that of other groups selected from consecutive clinic cases according to their fat distribution, age and clinically apparent endocrinopathy.

The mean basal metabolic rate is lower in the obese (minus 6.33 plus or minus 0.8) and significantly lower (minus 10.5 plus or minus 1.1) in pituitary obesity as well as in obese juveniles (minus 12.7 plus or minus 1.1). Distribution curves also show a greater frequency of rates below minus 10 in both these groups.

The specific dynamic action of proteins, determined by the sample method after ingestion of a small protein meal, is lower than in previously reported normal controls (8.28 plus or minus 0.68). A higher specific dynamic action (11.0 plus or minus 1.77) appears in obese patients of even fat distribution and in those with regional distribution of the hypothyroid or hypogonad type (11.1 plus or minus 0.85). The specific dynamic action is definitely low in pituitary obesity (4.17 plus or minus 0.42) as well as in the juvenile group (4.9 plus or minus 0.76). Much higher values were obtained in the menopausal or hypogonad group (15.9 plus or minus 1.43). The differences observed are statistically significant.

The mean of the fasting blood sugar in the obese (101 plus or minus 1.35 mgm. %) is normal, but the

distribution of the figures surveyed shows a substantial percentage in the hypoglycemic and hyperglycemic ranges. The mean blood sugar in pituitary (94.4 plus or minus 1.6) and juvenile obesity (93.6 plus or minus 1.58) is significantly lower.

The blood uric acid is elevated in the obese; for the mean in 100 unselected cases is 3.65 plus or minus 0.08 mgm. %. A significantly higher mean (3.97 plus or minus 0.09 mgm. %) was obtained in pituitary obesity.

Lymphocytosis is a symptom of obesity, according to the mean of 100 unselected cases (35.4 plus or minus 0.7). Even greater lymphocytosis prevails in the pituitary group (40.0 plus or minus 0.63%); the difference is statistically significant.

Lower 24 hour urine volume and diminished salt

excretion characterize both the unselected (980 plus or minus 42 cc., and 8.6 plus or minus 0.45 Gm.) and the pituitary type of obesity (1090 plus or minus 55.2 cc., 9.5 plus or minus 0.49 Gm.).

On performance of the salt tolerance test water and salt are retained in both groups, but especially in the pituitary type; the difference of the means of salt excretion is statistically significant.

CONCLUSION

The figures presented seem to indicate that deviations from the normal metabolic state are so common in the obese as to assume statistical significance. The metabolic state is even more abnormal in obese juveniles and in patients whose fat distribution and clinical symptoms suggest pituitary disease.

REFERENCES

1. Boughby, W. M. & J. Sandiford: *J. Biol. Chem.*, 51:753, 1922.
2. Conn, J. W.: *Physiologic Rev.*, 24:31, 1944.
3. Dougherty, T. F. & A. White: *Endocr.*, 35:1, 1944.
4. Fryberg, R. H. & L. H. Newburgh: *Arch. Int. Med.*, 58:229, 1956.
5. Goldzieher, M. A.: *Assn. Res. Nerv. Ment. Dis.*, 17:536, 1938.
6. Goldzieher, M. A.: *The Endocrine Glands*. D. Appleton Century, 1939.
7. Goldzieher, M. A.: *Clinics*, 1:1060, 1943.
8. Goldzieher, M. A. & M. B. Gordon: *Endocr.*, 17:569, 1933.
9. Goldzieher, M. A. & S. Slatkivitz: *J. Cl. Endocr.*, 3:37, 1943.
10. Gradwohl, R. B. H.: *Clinical Laboratory Methods*, Mosby Co., St. Louis, 1935.
11. Means, J. H.: *J. Med. Res.*, 32:121, 1915.
12. Newburgh, L. H.: *Physiologic Rev.*, 24:21, 1944.
13. Rony, H.: *Obesity and Leanness*. Lee & Febiger, Phila., 1941.
14. Rose, A. W.: *Endocr.*, 12:1, 1928.
15. Rose, A. W. & C. H. Lawrence: *Endocr.*, 12:235, 1928.
16. Strang, J. M. & H. B. McClungage: *Am. J. Med. Scs.*, 182:49, 1931.
17. Todd, J. C. & A. H. Sanford: *Clinical Diagnosis*, Saunders Co., Philadelphia, 1932.
18. Wherry, L. E. H. & C. J. C. Britton: *Disorders of the Blood*, Blakiston, 1942.

Effect of Temperature on the Experimental Production of Ulcers in the Intestines of Dogs

By

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IN previous communications we have described the effect of various chemicals (1), concentration of pepsin (2), and hydrostatic pressure (3) on the experimental production of ulcers in the intestines of dogs. In other papers it was shown that pepsin is probably not the only enzyme to be considered as etiologically significant in "peptic" ulcers (4,5). The

results of these studies and the fact that the activity of enzymes is a function of temperature led us to believe that it would be of interest to study the effect of temperature on ulcer production.

The procedure used has been described in detail were exposed to a 0.1 per cent pepsin in N/10 HCl in (3) except that in these studies intestinal loops solution at only one hydrostatic pressure, namely, 90 cm. H₂O. Also in these experiments, thermometers were introduced in both the proximal and distal ends of the intestinal loops by means of T-cannulae for recording the actual temperatures in the loops. The solution was run through the loop until the desired temperature, i. e., either 5, 25, 40, or 45 degrees C, was obtained throughout its length. Briefly, the technique consists simply in exposing isolated loops of the intestines of anesthetized dogs to a solution for a certain time, at the end of which the gut is examined grossly and microscopically for damage.

The temperatures in degrees C at which the solutions were introduced were 5, 25, 40 and 45. The solutions in the loops were renewed at one half hour or hour intervals until perforating ulcers occurred. The results are given in Table I.

It should be pointed out that the temperatures listed in Table I were the temperatures at which the solutions

TABLE I

Effect of Temperature on the Production of Perforating Ulcers in Intestinal Loops Exposed to 0.1 per cent Pepsin in N/10 HCl under Hydrostatic Pressure of 90 cm. H₂O.*

Temp. of Solution	No. Dogs	Interval at Which Solution Was Renewed (Hrs.)	Time Exposed (Min.)	Average	Range
5	6	½	176	90 - 270	
5	6	1	133	82 - 210	
25	10	1	82	60 - 90	
40	12	1	77	44 - 126	
45	10	1	64	33 - 111	

* Merck, N. F. Powdered

were introduced and that these solutions in time assumed the temperature of the body. This rate of change is given in Table II.

TABLE II
Rate of Change of Temperature in Degrees C of Solutions in Dogs' Intestines.

Time (Min.)	Temperature of Solution at Beginning			
	5	25	40	45
0	5	25	40	45
3	16	30	38	42
10	26	34	37	40
20	31	34	35	36
30	33	34	34	34

The average time for perforating ulcers to occur clearly demonstrated that the lower the temperature the less the digestive effect of the enzyme solution on the intestinal mucosa. In half the experiments where the temperature of the solution was 5°C, the solution was renewed at one half hour instead of one hour. The result of this cooling was to increase the time for perforation from 133 minutes to 176 minutes.

SUMMARY

The digestive action of a 0.1 per cent pepsin in N/10 HCl solution on intestinal mucosa was reduced by lowering the temperature of the solution.

REFERENCES

- Driver, R. L., Dorier, G. S. and Denham, H. C.: Effect of Various Chemical Agents Affecting Permeability of the Mucosa on the Formation of Ulcers. *Science*, 1943, 95:158
- Driver, R. L., Chappell, R. H. and Garin-Chesa, E. B.: Effect of Concentration of Pepsin and the Differential Susceptibility of Jejunal Segments to Experimental Jejunal Ulcers in the Dog. *Amer. Jour. Dig. Dis.*, 1943, 12:168
- Driver, R. L., Chappell, R. H. and Garin-Chesa, E. B.: Effect of Hydrostatic Pressure on the Experimental Production of Ulcers. *Amer. Jour. Dig. Dis.*, 1943, 12:168
- Driver, R. L.: Comparative Efficacy of Pancreatin and Pepsin in the Experimental Production of Ulcers in the Intestines of Dogs. *Arch. Path.*, 1945, 30:34
- Driver, R. L.: A Study of Ulcer Production in the Intestines of Dogs by Various Enzymes under Hydrostatic Pressure. *Proc. Soc. Exper. Biol. and Med.*, 1945, 59:281

The Inhibitory Effect of Mineral Oil on the Experimental Production of Ulcers

By

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In previous communications (1, 2, 3) results were reported on the effect of various chemicals, concentration of pepsin and hydrostatic pressure on the experimental production of ulcers in the intestines of dogs. These investigations led to the belief that the severity of ulceration could be decreased by a substance which protects the mucosa from the digestive action of pepsin and HCl. That mineral oil might have such a protective influence was suggested by the fact that this agent inhibits absorption, apparently by coating the mucous membrane. For this reason the use of mineral oil immediately before or after meals is not recommended.

The purpose of the investigations reported here was to find out if mineral oil decreases the severity of necrosis in the gastrointestinal tract brought about by pepsin in HCl.

METHODS

The abdomens of 49 dogs under Dial-nrethane anesthesia* were incised and in each dog a loop of intestine about 18 inches long was selected reaching from about the mid-portion of the duodenum to about 12 inches below the ligament of Treitz in the jejunum (3). Each end of the loop was cannulated for the introduction and withdrawal of the solution to be tested. After washing out the loop with 500 cc. of H₂O, the solution, which was 0.1 per cent pepsin in N/10 HCl, was introduced into the loop and allowed to remain there for 6 to 12 hours or until perforation occurred.

The loop was then removed and examined grossly and microscopically for damage.

The method adopted in this laboratory (2) for evaluating the degree of damage is described as follows: (1) represents a condition in which there is a slight surface necrosis of the mucosa. (2) designates a deeper necrosis involving at least 1/3 of the thickness of the mucosa of the entire area with smaller areas (from 1/2 cm.² to 2 cm.²) showing necrosis as deep as the submucosa. (3) indicates necrosis of practically all the mucosa with some patches extending into the circular muscle. (4) was applied to a loop having necrosis extending to the serous coat or to a frank perforation. For each set of experiments the average was taken of loops scored in this manner.

In one group of dogs the solution was allowed to flow through the loop at the rate of 2 cc. per minute under zero cm. pressure. In another group the solution was in contact with the mucosa of the gut at 90 cm. H₂O pressure and was renewed every hour. In each of these groups some loops were treated with mineral oil and some were not. The latter loops served as controls. The loops treated with mineral oil were filled with the oil at the beginning of the experiment and allowed to remain that way for 15 minutes under zero pressure. At the end of this time the oil was washed out with 200 cc. of the pepsin-HCl solution and exposed to the solution as stated above, i. e., either under zero or under 90 cm. H₂O pressure. Also in the oil treated loops at every hour, 50 cc. of the oil were run through in a few seconds, immediately washed out with 200 cc. of pepsin-HCl solution and

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The Dial-nrethane was generously supplied by the Ciba Pharmaceutical Products Inc., Summit, New Jersey.
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the experiment continued. The results are given in Table I.

TABLE I

Comparison of Damage Caused by 0.1% Pepsin in N/10 HCl on the Mucosa of Intestinal Loops Treated and Untreated with Mineral Oil.***

ZERO PRESSURE			
	No. Dogs	Time Exposed	Severity
		Average Range	
		Min. Min.	
Untreated	15	700 390-810	1.9
Treated	12	700 390-780	0.6

90 cm. H ₂ O PRESSURE			
	No. Dogs	Time Exposed	Severity
		Average Range	
		Min. Min.	
Untreated	10	82 60-90	4.0
Treated	12	130 89-230	4.0

* Merck; N. F. Powdered

** Minolene, Heavy Mineral Oil, Purepac Corp.

Perforation occurred in all dogs where the pressure of the pepsin-HCl solution was 90 cm. H₂O. However,

the time for the perforation to appear was increased from 82 minutes for the loops not treated with mineral oil to 132 minutes for those treated. This represented an increase of about 60 per cent.

When the pressure was zero no perforations occurred but the severity of damage was decreased from 1.9 to 0.6. In eight of these dogs there was no damage at all.

These results constitute a confirmation of the previous finding that an increase in the permeability of intestinal mucosa leads to increased digestion of the mucosa by pepsin (1). It is very probable that the mineral oil forms a protective coating over the mucosa preventing the penetrability of pepsin and acid and thereby decreasing digestion.

SUMMARY

1. Intestinal loops of dogs were exposed to a 0.1 per cent pepsin in N/10 HCl solution under zero pressure or 90 cm. H₂O pressure. In each of these groups some loops were treated with mineral oil and some were not.

2. Mineral oil markedly inhibited the digestive action of 0.1 per cent pepsin in N/10 HCl on the mucosa of the small intestines.

REFERENCES

- Driver, R. L., Dozier, G. S. and Denham, H. C.: Effect of Various Chemical Agents Affecting Permeability of the Mucosa on the Formation of Ulcers. *Science*, 1942, 98:158.
- Driver, R. L., Chappell, R. H. and Carmichael, E. B.: Effect of Concentration of Pepsin and the Differential Susceptibility of

- Jejunal Segments in Experimental Jejunal Ulcers in the Dog. *Amer. Jour. Dig. Dis.*, 1915, 12:166.
- Driver, R. L., Chappell, R. H. and Carmichael, E. B.: Effect of Hydrostatic Pressure on the Experimental Production of Ulcers. *Amer. Jour. Dig. Dis.*, 1915, 12:168.

The Importance of Paracolon Organisms with *Salmonella* and *Shigella* Antigens

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THE microorganisms causing diarrhea may be divided into several groups, including bacteria, viruses, parasites and mycotic agents. While there has been considerable discussion concerning the significance of the presence of certain molds, yeast and viruses in the intestines, the parasitic incitants of diarrhea are well known and, with the exception of a few protozoa of questionable pathogenicity, there is a general agreement as to which organisms can be considered as possible causes of intestinal disturbances.

There is little doubt as to the pathogenic power of *Vibrio comma*, *Eberthella typhosa*, *Salmonella* (paratyphoid-enteritis organisms) and most of the *Shigella* (dysentery bacilli), but many other organisms such as *Proteus*, paracolon bacilli, *Pseudomonas* and *Alcaligenes faecalis* are being regarded with varying attitudes by different groups of investigators, some of whom consider them as harmless, others as secondary invaders and still another as potential pathogens. The paracolon organisms during recent years have been at-

tracting the attention of both laboratory workers and physicians, due to certain peculiar characteristics which place these microbes between the highly pathogenic *Elberthella-Salmonella-Shigella* and the non-pathogenic *coli-aerogenes* groups. They are rarely found in healthy individuals, but appear mostly in diarrheic stools in which known intestinal pathogens are or are not present. Biochemical and serological studies of the paracolon organisms led to confusing results due to their widely varying reactions.

Stuart et al. (1) were the first in this country to establish a firm basis for the differentiation and interpretation of paracolon organisms. They defined this group as bacteria showing the morphological characteristics of *colon-aerogenes* bacilli: mostly motile; many strains forming hydrogen sulfide; fermenting dextrose and mannitol; and slowly attacking one or more of the following substances: lactose, sucrose, salicin; revealing IMViC responses according to which subgroups can be set up as coliform, aerogenes-like and intermediate. In addition to these subgroups, anaerobic forms, i. e., those that form acid, but not gas, from fermentable substances, have to be differentiated. Some

strains seem to be able to cause diarrhea.

The work of Stuart et al. (1), Sandiford (2), Parr (3), Shiff et al. (4), Peluffo et al. (5), Saphra and Silverberg (6), Lauppold (7), Rhodes (8), Neter and Clark (9, 10) shed much light upon the problem of the pathogenicity of paracolon bacilli. However, it is a problem which has still not been satisfactorily solved. One of the most interesting factors to be considered in any investigation of this question is the presence of Salmonella and Shigella antigens in some paracolon strains. It is to be noted that none of the above authors was able to discover a relationship between the biochemical behavior, antigenic structure and pathogenicity of the paracolon organisms.

During the past four years more than 1,200 paracolon organisms were subjected to study by the authors of this paper. They were isolated from inmates of Illinois State Hospitals, patients of the Chicago Free Dispensary, students of The Chicago Medical School and sent in by other laboratories for differentiation. Only 33 strains (from 10 cases and outbreaks) of the 1,200 strains examined contained Salmonella "O" or Shigella antigens. The history of the cases or outbreaks, together with the bacteriological findings, is given below.

Case No. 1 was a 36 year old woman who was a chronic carrier of *Salmonella montevideo* VI, VII: gms₁₂₂. Three months after the last isolation of *S. montevideo*, organisms were found which were motile, formed hydrogen sulfide and fermented lactose slowly. Sucrose or salicin were not fermented. These bacteria were indol negative; methyl red, Voges-Proskauer and citrate positive; i. e., they presented IMViC (-+++). Further investigation revealed that they possessed parts of VI, VII of the *Salmonella "O"* antigens. Reexamination after a two weeks interval showed neither *Salmonella* nor paracolon organisms in the stool.

The picture presented in this case is comparable to that observed by Stuart et al. (11) during an outbreak of *Sh. alkalescens* dysentery when transitional organisms from *Sh. alkalescens* to *E. coli* were found.

Case No. 2 was a six-months old child who had a diarrhea lasting for several days. No blood, but much mucus, was present in the light-colored stools. No intestinal protozoa and no *Salmonella* were found. The strain of paracolon bacilli isolated from the patient was forwarded to this center by a laboratory which suspected the presence of *Shigella*.

This strain of paracolon organism was motile, formed hydrogen sulfide, fermented lactose and sucrose slowly, but did not attack salicin. The IMViC reaction was (+---). Serological analysis revealed the presence of VI, VII of the *Salmonella "O"* antigens.

It was impossible to obtain a second stool specimen or a detailed story of the case.

Cases No. 3 and 4 were students who ate their meals in low class restaurants. In both cases the diarrhea began at night. Light colored, fluid to semi-fluid stools were passed without tenesm. No fever or vomiting was reported. The condition ended in 24 hours without complications. No known pathogenic organisms were

found in the stools upon bacteriological and parasitological examination.

From Case No. 3 motile, hydrogen sulfide forming paracolon organisms were found, which slowly fermented salicin. They revealed the IMViC structure (-+--). Parts of *Salmonella "O"* I and XII antigens were discovered.

In Case No. 4, motile, non-hydrogen sulfide forming, slow lactose fermenting paracolon bacilli with the IMViC structure (+---) were found. *Salmonella* antigens VI and XIV were present.

Paracolon bacteria were not recovered from these cases upon reexamination after three days.

Case No. 5 was a 46 year old woman from the south side slums of Chicago, who visited the clinic because of periodic diarrhea. She reported soft, yellowish stools occurring three to four times daily. There was no tenesm or fever, but a dull pain was present in the upper abdomen. This condition was said to recur every three to four months, lasting at each occasion for some weeks.

The physical examination did not show apparent changes aside from the coated tongue and sensitivity to pressure around the McBurney point. The temperature and pulse were normal.

Stool specimens and rectal swabs from the patient revealed *Endamoeba histolytica* and paracolon bacilli. The latter were motile, did not form hydrogen sulfide and slowly fermented lactose. The IMViC structure was (-++). Parts of I and VI of the *Salmonella "O"* antigens were present.

The organisms disappeared from the stool after antimicrobial treatment with Vioform and Carbarsone.

No. 6 was an outbreak of diarrhea among a group of people attending the same party. Fruit salad, cream cake, and sandwiches made of cream cheese and chicken salad were served. Approximately 60 people attended. The day was hot, the temperature being about 90° F. The food was prepared approximately three hours prior to serving and was eaten between 3 P. M. and 5 P. M. Symptoms developed between 4 A. M. and 6 A. M. the following morning. Nearly a dozen of the participants had severe diarrhea lasting in one case as long as 18 hours, severe abdominal pains, but no vomiting. The stools were reported "greenish" or "yellowish". There was no tenesm. The victims were not checked for temperatures. All who became ill had eaten chicken salad sandwiches.

Unfortunately none of the food was available for examination. Only one of the participants was seen while the diarrhea was still present.

No protozoa and no *Staphylococci* or *Streptococci* of the food poisoning type could be isolated from the stool of the person who still had diarrhea. Paracolon organisms were very numerous and belonged to one strain. This strain was motile, fermented sucrose and salicin slowly, did not form hydrogen sulfide and showed an IMViC pattern (-+-+). Parts of the *Salmonella "O"* antigens I and VI were discovered.

Outbreak No. 7 occurred in a State Hospital. 27 attendants out of 31 who ate chicken soup became ill 7 to 10 hours after the food was eaten. The soup had

been prepared six hours before consumption and not chilled. The symptoms were cramps, some tenesmus and profuse diarrhea. No food sample was available for examination. The local bacteriologist isolated *Proteus morganii* type I and paracolon organisms from all the stools from which cultures were forwarded for identification. The paracolon bacilli were motile, produced some hydrogen sulfide, fermented sucrose and salicin slowly, and revealed an IMViC pattern (-+++). *Salmonella "O" antigens I and XIII* were present.

Cases No. 8 and 9 were presented by a municipal Health Department Laboratory*. Both cases were patients with long standing diarrhea. The cultures were motile, did not produce hydrogen sulfide, fermented lactose slowly, had an IMViC pattern (-+-+) and gave agglutination with *Salmonella "O"* antisera VI, VII, XIII and *Shigella* 3, 4 and 7 antisera.

Case No. 10 was a 27 year old man who suffered from constipation which was interrupted every month or six weeks by an outburst of diarrhea lasting for three to five days. There were uncertain pains in the lower abdomen, lack of appetite and "nervousness". Examination revealed a coated tongue, sensitivity over the colon ascendens on pressure and typical amebic ulcers upon proctologic investigation.

The stool contained *Endamoeba histolytica*, *Endolimax nana*, *Proteus vulgaris* and paracolon bacilli. Some of these organisms followed the typical pattern of slow lactose and sucrose fermenting, motile, non-hydrogen sulfide forming Paracolon aerogenes. Others differed by giving an IMViC reaction (+---) and having *Salmonella "O" antigens IV and XIII*.

The paracolon organisms disappeared after antiamebic treatment with Vioform and Carbarsone.

While this series of observations is not of sufficient scope to be of value from the taxonomic point of view, the authors wish to emphasize the absence of paracolon organisms manifesting *Salmonella* or *Shigella* antigens in persons having an intact bowel. They were unable to recover such bacilli from more than 7,000 stools from healthy persons examined during the same period of time.

Attention is called in Case No. 1 to the possibility of bacterial variation with the appearance of transitional forms between *Salmonella* and coliforms. In considering the histories of the cases and outbreaks observed the question arises as to whether the occurrence of paracolon bacilli manifesting *Salmonella* and *Shigella* antigens is not a postlude to a true *Salmonella* infection from which typical *Salmonella* have disappeared. Such variants were not encountered in this

*Mr. C. W. Anderson, Director of the Laboratories of the Municipal Health Department of Rockford, Illinois, sent two more strains with the same antigens while this paper was in print. Both came from patients with severe diarrhea, mucus in the stools, pain.

study at any time while the acute diarrhea was in progress nor was any account of such circumstance found in the literature. Usually the disappearance of *Salmonella* from a case or carrier is forecast by the appearance of rough forms. However, even if we suspect cases No. 2, 5, 6 and possibly also 10 as harboring paracolon organisms with *Salmonella* antigens as an aftermath of a *Salmonella* infection, Nos. 3 and 4 were examined early manifestations of diarrhea, only a few hours after the beginning, during which period variants would scarcely have had time to occur. No reasonable explanation can be given for the presence of paracolon organisms with both *Salmonella* and *Shigella* antigens in Cases 8 and 9 if only the loss-variant theory is accepted for the elucidation of the problem of *Salmonella* or *Shigella* antigens occurring in paracolon bacilli. From the evidence presented in these cases the authors conclude that there may be a direct connection between the paracolon organisms themselves and symptoms of dysentery.

SUMMARY

Of 1,200 paracolon organisms isolated from different sources, only 33 strains originating from ten cases manifested *Salmonella "O"* or *Shigella* antigens. One such strain having antigens VI, VII appeared in a chronic carrier of *S. montevideo* after the person ceased to be a carrier of *Salmonella*. Antigens VI, VII occurred in another strain isolated from an infant with diarrhea. Two strains, with antigens I, XII and IV, XIV, respectively, were isolated from acute diarrheas suspected of being caused by food poisoning. A strain with antigens I, VI and another with antigens IV, XIII were found in patients together with *Endamoeba histolytica*. Antigens I, VI and I, XIII, respectively, were present in two strains found in food poisoning outbreaks, the latter being associated with the appearance of *Proteus morganii*. In two cases of diarrhea in the same locality identical paracolon strains containing *Salmonella* antigens VI, VII, XII and *Shigella* antigens 3, 4, 7, simultaneously, were isolated.

The occurrence of transitory forms between *Salmonella* and colon-aerogenes bacilli in stools from which *Salmonella* have disappeared, is discussed. It is sustained, however, that paracolon organisms have to be recognized as potential pathogens.

ACKNOWLEDGEMENTS

The authors are indebted to Dr. P. R. Edwards, Director of the National *Salmonella* Center, University of Kentucky, Lexington, Ky., and to Dr. V. K. Wheeler, Research Microbiologist, Connecticut Department of Health, for their help in the analysis of strains No. 1, and 8 and 9, respectively.

REFERENCES

1. Stuart, C. A., Wheeler, K. M., Rustigian, R. and Zimmerman, A.: Biochemical and Antigenic Relationships of the Paracolon Bacteria. *J. Bact.*, 43:101-119, 1943
2. Sandiford, B. R.: The Paracolon Group of Bacteria. *J. Path. and Bact.*, 41:77-88, 1935
3. Parr, L.: Coliform Bacteria. *Bact. Review*, 3:1-48, 1939
4. Shiff, F., Bornstein, S. and Saphra, J.: The Occurrence of *Salmonella "O"* Antigens in Coliform Organisms. *J. Immunol.*, 10:365-372, 1941
5. Peffatio, A., Edwards, P. R. and Bruner, W. F.: A Group of Coliform Bacilli Serologically Related to the Genus *Salmonella*. *J. Inf. Dis.*, 70:185-192, 1942
6. Saphra, J. and Silverberg, M.: Taxonomy of *Salmonella-like* Coliform Organisms. *J. Immunol.*, 44:129-133, 1942
7. Luippold, G. F.: Typhoid Vaccine Studies. Part V. *Amer. J. Hyg.*, 36:334-361, 1942
8. Rhodes, A. J.: A Small Outbreak of Diarrhea Associated with the Paracolon Bacillus. *J. Hyg.*, 42:399-402, 1942
9. Neter, E. R. and Clark, P.: The Effectiveness of Different Culture Media in the Isolation of Enteric Microorganisms. *Amer. Jour. Dig. Dis.*, 11:223-238, 1944
10. Neter, E. R. and Clark, P.: Observations on the Possible Pathogenicity of Paracolon Bacilli as Incitants of Diarrheal Diseases in Infants and Children. *Amer. Jour. Dig. Dis.*, 11:356-360, 1944
11. Stuart, C. A., Rustigian, R., Zimmerman, A. and Corrigan, F. V.: Pathogenicity, Antigenic Relationships and Evolutionary Trends of *Shigella Alkalescens*. *J. Immunol.*, 47:425-437, 1942

Staphylococci in Gastroenterology

By

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NEW YORK, N. Y.

WITH the exception of *staphylococcus* food poisoning, staphylococci are rarely considered in gastroenterology. This is probably due to the inadequacy of bacteriologic methods because it has long been suspected that the incidence is higher than, e. g., the 2 to 6 per cent reported in chronic invalids by Stiles and Chapman (1).

The discovery of better methods for isolating and testing staphylococci and the discovery by Koch (2) that with rare exceptions only staphylococci grow on an agar medium containing 7.5 per cent sodium chloride, have thrown new light on the relation of staphylococci to gastroenteritis.

It is now generally recognized that power to clot blood or plasma is associated with pathogenicity of the cultures but unless certain precautions are taken only cultures with strong coagulating power will give positive results. A technic of proved efficiency will be described later.

Applying these methods, particularly to gastroenterology and rhinolaryngology, the author (3) developed an agar culture medium for the isolation of pathogenic staphylococci that has given satisfactory results, the organisms being recovered from about one-third of the fecal samples from chronic invalids, most of whom had gastroenteritis. The medium consists of Bacto phenol red mannitol agar to which is added 75 grams of sodium chloride per liter. Because all other bacteria are eliminated, staphylococci grow as luxuriantly as they do in pure cultures on usual culture media. Moreover, pathogenic types are differentiated from nonpathogenic ones, the former producing normal sized colonies 99 per cent of which are surrounded by yellow zones of mannitol fermentation while the nonpathogenic types produce minute colonies without yellow zones. This differentiation is so reliable that 96 per cent of the cultures isolated were staphylococci that clotted plasma.

The method for isolating and testing staphylococci is as follows: The fecal sample is diluted 1:10 with sterile water and 0.01 ml of this is plated on the sodium chloride phenol red mannitol agar. Meanwhile, the solid content of the diluted feces is determined, because calculations are on the basis of dry weight. The inoculated plates are incubated exactly 36 hours and are then inspected for typical colonies. The number is noted and is calculated on the basis of millions per 100 grams

of dry feces. The colonies are transplanted to proteose lactose agar (Difco) to which has been added 75 grams of sodium chloride per liter, spread, and incubated exactly 10 hours. The coagulase test is then applied as follows: A loopful of the growth is scraped into a platinum loop and is mixed with 0.3 ml of broth. When the culture is grown on the sodium chloride proteose lactose agar there is enough sodium chloride in the culture mass for the test but when the culture is grown on other media then the broth must contain sodium chloride. The bacterial suspension in broth is stirred thoroughly and is then mixed with 0.3 ml of fresh oxalated or citrated human whole blood which has been tested with a weakly coagulating culture to be sure that it gives a satisfactory clot. The mixture is put in the incubator and is inspected in 1, 2 and 3 hours. If no clot forms the tube is left on the laboratory table overnight and inspected again. The cultures that clot under these conditions are probably pathogenic, with a high degree of precision.

Plasma coagulating staphylococci were found in 31 of 102 fecal specimens in numbers ranging from 1 to 62 millions per 100 grams of dry feces, the average being 9 millions. That most of them were washed into the gastrointestinal tract from the upper respiratory tract is indicated by the fact that when the fecal culture was negative, plasma coagulating staphylococci were absent in the nose and throat cultures in 55 per cent (when there was only one colony on a plate it was ignored as a probable contaminant) but when the fecal culture was positive plasma coagulating staphylococci were absent in the nose and throat cultures in only 5 per cent. Hence, when plasma coagulating staphylococci are found in feces, the upper respiratory tract should be checked. Elimination of the staphylococci from these foci will often cure the gastroenteritis, assuming that intestinal pathogens have been ruled out. Other cases will respond when the associated streptococci have been eliminated.

One striking example of the value of such bacteriologic study concerns a boy who had "dysentery" for several years and who had been treated unsuccessfully by excellent gastroenterologists. On finding pathogenic staphylococci in the feces, *staphylococcus* toxoid was given and the diarrhea stopped the day after the first injection.

R E F E R E N C E S

1. Stiles, M. H. and Chapman, G. H.: Probable Pathogenic Streptococci and Staphylococci in Chronic Low Grade Illness. An Analysis of Their Frequency in Three Hundred and Ninety Five Cases. *Arch Otolaryngol*, 31:458-466, March, 1940

2. Koch, F. E. *Electivnährboden für Staphylokokken*. Zentralbl Bakteriol 1 Abt, 149:122-124, 1942
3. Chapman, G. H.: The Significance of Sodium Chloride in Studies of Staphylococci. Jr. Bact., 50:201-203, (August) 1945

Book Reviews

What to do About Vitamins. By Roger J. Williams. Pp. 56, (\$1.00). Norman, University of Oklahoma Press, 1945.

The alphabetical blast which greets the radio listener and newspaper reader when the subject of vitamins is being discussed (usually in some sales-promotion talk) recalls the alphabet soup of nursery-school days. Vitamin sales have reached the two hundred million dollars per year level so one may well suppose that indeed a potent "racket" has developed. Between the individual who says "my grandfather lived to reach 99 without even hearing about vitamins" and the individual who can't wait to finish his last bottle of "Make-Eau-Strong Pills" before hurrying to purchase another, there are the limitless wastes inhabited by the cautious and puzzled.

In this little book the facts about vitamins are set forth in an arresting manner. The book is really a pleasant surprise. Doctor Williams is one of the foremost authorities on vitamins living and it is no secret that with few exceptions authoritative scientists do not write like scientific authorities for the layman. Doctor Williams is one of the exceptions. This book is very readable and free of the errors commonly found in other science books for the layman. The viewpoint expressed is new and much of the information is new, coming from Doctor Williams' own laboratory. A novel presentation is the series of graphs showing the caloric and vitamin values of various foodstuffs. This book may be recommended by the physician to his patients who are interested in the question of vitamins and what to do about them.

New Goals for Old Age. Edit. by George Lawton. Pp. 210, (\$2.75), New York, Columbia University Press, 1945.

The life expectancy of the new born has increased since the turn of the century by about twenty years. This of course does not mean that the present-day child will live twenty years longer than did his grandfather. The better medical and public health care practiced these days has resulted in a reduction in infant mortality so that the infant of these times has a better chance of reaching an advanced age. This of course means that with time the number of aged people living will increase because conditions for their reaching an old age become easier. Lawton says that today we have nine million people in this country who are over sixty-five years of age and estimates that by 1980 the number will have reached twenty-six million.

What shall be done about the aged who are in our midst? Should they be put away in "the cave from which none returned", as the tale (told in the prologue) recounts was the practice long ago in Asia Minor? The problem is with us today and we do not think that wars and atom bombs will affect the conditions creating the problems.

Aging brings certain changes in physical and men-

tal capacities but not all these changes are on the debit side. Our care for the aged should not be a matter of duty towards ancestors. It should be a matter of public interest to see that aged people fit into society as integral parts of it and that society be educated to recognize that it must utilize all of its citizens to the maximum limits of each.

The contributors to this book are social science students, psychiatrists, physicians, and social service workers who have spent many years studying the problems of aging and the aged. All the essays are well written and interesting. The volume contains an excellent bibliography. This book should be required reading for all social service workers and others whose activities or interests are in the field of growth and senescence.

Essentials of Body Mechanics in Health and Disease. By J. E. Goldthwait, L. T. Brown, L. T. Swaim and J. G. Kuhns. Pp. 337, (\$5.00). Philadelphia, J. B. Lippincott Co., 1945.

Many of our chronic patients yield on examination only negative findings relating to basal metabolism, blood, renal functions, or visceral roentgenology. The patient is nevertheless ill and the tendency among some clinicians is to dismiss the case as one with a "functional condition." While anatomy has been considered a foundation of medicine, the impression has grown that all bodies conform to the single human type considered normal. Practically none of the chronic disease patients is structurally normal when contrasted to the type specimen. It thus becomes important to learn what structural changes the body of the chronic patient may show. Often these changes may be the only variation from good health that can be measured in terms of physical units.

The present volume is the fourth edition of a book originally written in 1934 and titled "Body Mechanics in Health and Disease." The purpose of the book appears to be well fulfilled. The body types and body mechanics under a variety of disease conditions are discussed and exemplified with numerous illustrations. Certainly the problem of diagnosis is greatly enlightened, at least for teaching purposes in clinics, by this book. The brief chapter on "Angina Pectoris and postural emphysema related to obesity" by William Kerr is interesting. The gastroenterologist will find the chapters on "Diseases of the abdominal viscera" and "Cases with visceral disturbances" well worth reading. "Geriatrics and body mechanics" is a subject that might well have been extended to twice its length.

This book will be found interesting reading by the senior medical student and general practitioner alike. It should prove valuable to all those dealing with either the chronic patient or the patient with physical deformities. The specialist in physical medicine probably will find particularly useful the sections on chronic arthritis, foot and body mechanics, and treatment by muscle re-education. A short selective bibliography is included.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Medicofilm Service of the Army Medical Library at 25c per each complete article not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Medicofilm Service, Army Medical Library, Washington, D. C.)

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CLINICAL MEDICINE

STOMACH

ROBERTSON, E. M.: *Gastric excretion of neutral red*. (*Glasgow Med. J.*, v. 25, p. 158, Feb. 1945).

Neutral red excretion as a test of parietal cell function was studied in normal individuals and patients with various gastrointestinal diseases. Non-gastric pathology cases had an excretion time ranging from 2 to 6 minutes. People with either gastric or duodenal ulcer had an excretion time between 0.5 and 2 minutes. In marked contrast in chronic gastritis, gastric carcinoma and pernicious anemia the excretion time was much longer than 6 minutes, sometimes being delayed indefinitely.—F. E. St. George.

HORAN, H. J. AND COMFORT, M. W.: *Inflammatory cyst of the stomach secondary to cholecystic disease. Report of a case*. (*Proc. Staff Meet. Mayo Clinic*, v. 20, pp. 237, 1945).

A fifty year old patient who previously had had a cholecystostomy with complaints of gaseous distress, mild colicky attacks, nervousness, fatigue and insomnia was seen at the clinic. Roentgenoscopy revealed an extrinsic tumor of the stomach. At operation the subacutely inflamed gall bladder was found attached at its fundus to a cystic mass arising from the wall of the stomach. The gall bladder contained a stone impacted in the cystic duct. Partial gastrectomy with Billroth I type of anastomosis and cholecystectomy was done. This represents a rare complication of cholecystic disease and appears to be the only case of this nature so far described in the literature.—Wm. J. Snape.

BOWEL

COLL, W. H.: *Carcinoma of the colon*. (*Rocky Mountain Med. J.*, v. 42, p. 169, 1945).

Fifty consecutive cases of carcinoma of the colon admitted to the hospital were studied. Obstruction, either partial or complete, was present in 60 per cent of the patients having the tumor on the left side and in only 16.6 per cent of those with the tumor on the right side. However, vomiting was noted to the same extent in both series of patients. The mortality rate was ten per cent, being higher (20 per cent) in patients over sixty-five years of age than in younger patients (nearly 7 per cent). One stage operation,

resection with primary anastomosis, is advocated when prevention of infection by sulfonamides or penicillin is used.—D. A. Wocker.

ULCER

THORNTON, T. F., STORER, E. H. AND DRAGSTEDT, L. R.: *Supra-diaphragmatic section of vagus nerves and gastric secretion in patients with peptic ulcer*. (*Proc. Soc. Exp. Biol. Med.*, v. 59, p. 140, June 1945).

The studies on gastric secretion were performed on 19 patients with duodenal ulcers both before and after division of all vagus fibers to the stomach. Observations were made on the following: (a) Continuous night secretion—these observations indicate that an abnormally large secretion of gastric juice commonly occurs in the empty stomach of ulcer patients in the absence of any of the usual types of secretory stimuli and that this excessive secretion is neurogenic in origin. (b) Gastric secretion in response to histamine—in these cases an abundant flow of gastric juice with high free acidity was obtained and there was no significant difference in either volume or acidity after vagus section. (c) Gastric secretion in response to caffeine—the stimulation was as marked after operation as before, and the general effect was less than that secured by histamine. (d) Gastric secretion in response to insulin—the stimulation was approximately the same as that obtained with caffeine. It was completely abolished after the vagus section except in one patient. (e) Gastric secretion in response to the sham meal—only 30% of the patients displayed a definite increase in volume and free acidity of the gastric juice in response to the sham meal before operation. None responded after operation.—I. H. Dougherty.

SURGERY

NEWTON, F. C. AND BLODGETT, J. B.: *Succinyl-sulfathiazole and intestinal suction in surgery of the large bowel*. (*Surg.*, v. 18, p. 200, August 1945).

The use of the Miller-Abbott tube and the use of chemotherapy agencies have been two noteworthy innovations in pre-operative preparation of the patient. Until recently proximal colostomy was being widely used prior to resection of the large bowel. The Miller-Abbott tube makes it possible to obtain the same relief of distension that colostomy brought about. Incidence

in infection of the resected area was lowered by the colostomy and the newer chemotherapy can likewise reduce infection.

The authors studied 114 cases of large bowel resection. The control group of 78 cases had primary colostomy performed while the test group of 36 cases had both preoperative and postoperative succinylsulfathiazole. The mortality in the control group was 19 per cent but only 3 per cent in the test group. Complications were present in 25 per cent of the test patients but in as high as 58 per cent of the control patients. Infection was reduced from 43 to 6 per cent of the cases when considered on the basis of similar operative procedures. The authors conclude that intestinal suction and succinylsulfathiazole have a distinct place in preoperative and postoperative care of the patient who is to be subjected to large bowel resection.—M. H. F. Friedman.

EXPERIMENTAL MEDICINE

PATHOLOGY

ELLINGER, F. P.: *Response of the liver to irradiation*. (*Radiol.*, v. 44, p. 241, March 1945).

The administration of phosphorus and irradiation with x-rays produce essentially similar kinds of liver damage. The hepatotoxic effects are seen only when the x-ray dosage is high enough to produce death in 70 to 80 per cent of the cases when irradiated once. If smaller doses of x-rays are used, then the liver damage is seen when the cumulative effects approach the total lethal effects with respect to mortality rate. The injurious effects are believed to be due to a combination of direct effects of the x-rays plus the indirect effects of histamine substances resulting from radiation.—I. M. Theone.

BARONOFSKY, I., MERENDINO, K. A., BRATRUD, T. E., AND WANGENSTEEN, O. H.: *Fate of intravenously injected fat: its role in the production of ulcer*. (*Proc. Soc. Exp. Biol. Med.*, v. 59, p. 231, June 1945).

Fat and its role in the production of ulcer when injected intravenously was studied in rabbits, dogs, cats, and guinea pigs. The authors found that fat emboli may cause gastric and/or duodenal ulcers. The presence of fat emboli after intravenous injection of fat was demonstrated in the lung, brain, kidney, and stomach. Its rate of disappearance on experimental animals was such that after four days it was found in sections of lung tissue in 41 per cent, brain 11.1 per cent, kidney 34.4 per cent and the stomach 3.7 per cent of the sections examined. On the contrary, in sections of those animals sacrificed within one to four days after the intravenous injection of fat, the incidence of demonstrable fat emboli in the same tissues was: lung 91 per cent, brain 61 per cent, kidney 73.9 per cent, and stomach 47.8 per cent.—I. H. Dougherty.

MERENDINO, K. A. AND OTHERS: *Length of apparent duodenojejunal loop in gastric resection a factor in stomal ulcers*. (*Proc. Soc. Exp. Biol. Med.*, v. 58, p. 226, March 1945).

Associated with Merendino in this study were Drs. B. G. Lanin, F. Kolouch, Sr., I. Baronofsky, S. S. Liton and O. H. Wagensteen. An incidence of gastrojejunial ulcers after extensive gastric resection is reported higher from some clinics than others. Possibly the length of the afferent duodenojejunal loop is a factor in protection against stomal ulcers. To test this the authors carried out experiments on 22 dogs. A 75 per cent gastric resection with Billroth II technique was performed. The length of duodenal loop used was either short or long. It was found that a long afferent duodenojejunal loop favored spontaneous stomal ulcer formation. In these animals the ulcers formed regularly if histamine in beeswax was administered. On the other hand a short afferent duodenojejunal loop protected effectively against ulceration. Translated in terms of human surgery, the authors advocate a short afferent duodenojejunal loop with a retrocolic anastomosis established at or proximal to the ligament of Treitz.—M. H. F. Friedman.

PATROLOGICAL CHEMISTRY

SHAFFER, C. B. AND CRITCHFIELD, F. H.: *Nitrogen and sulfur content of liver tissue in relation to carbon tetrachloride exposure*. (*Proc. Soc. Exp. Biol. Med.*, v. 59, p. 210, June 1945).

Albino rats were used in experiments to determine the nitrogen and sulfur content of liver tissue in relation to carbon tetrachloride exposure. The results of these experiments showed that the values for total nitrogen and total sulfur determined on dry, fat-free liver tissue of rats following repeated exposure to carbon tetrachloride vapor were slightly higher than those of rats maintained on the same diet, but not exposed. The nitrogen to sulfur ratios of the two groups, however, were not statistically different. The significance of these findings is discussed in relation to the general problem of the protection of the liver from toxic agents by sulfur-containing amino acids.—I. H. Dougherty.

METABOLISM AND NUTRITION

MENSEHIK, Z.: *Vitamin E and adipose tissue*. (*Edinburgh Med. J.*, v. 51, p. 486, Dec., 1944).

The relation between vitamin E and metabolism of lipids was studied by either producing vitamin E deficiencies or administering the vitamin. A definite relationship was observed in mice between the amount of vitamin E ingested and the distribution of adipose tissue. Adipose tissue from subcutaneous and subperitoneal areas disappeared in female mice kept for several months on a diet deficient in vitamin E. Conversely the addition of vitamin E to diets increased greatly the amount of fat deposited in these depot regions. Nothing is known about a possible similar connection between vitamin E and fat metabolism and distribution in man.

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